MEGIN

Book of Abstracts - MEG Studies

Magnetoencephalography 2020–2022

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Forewords

Dear reader,

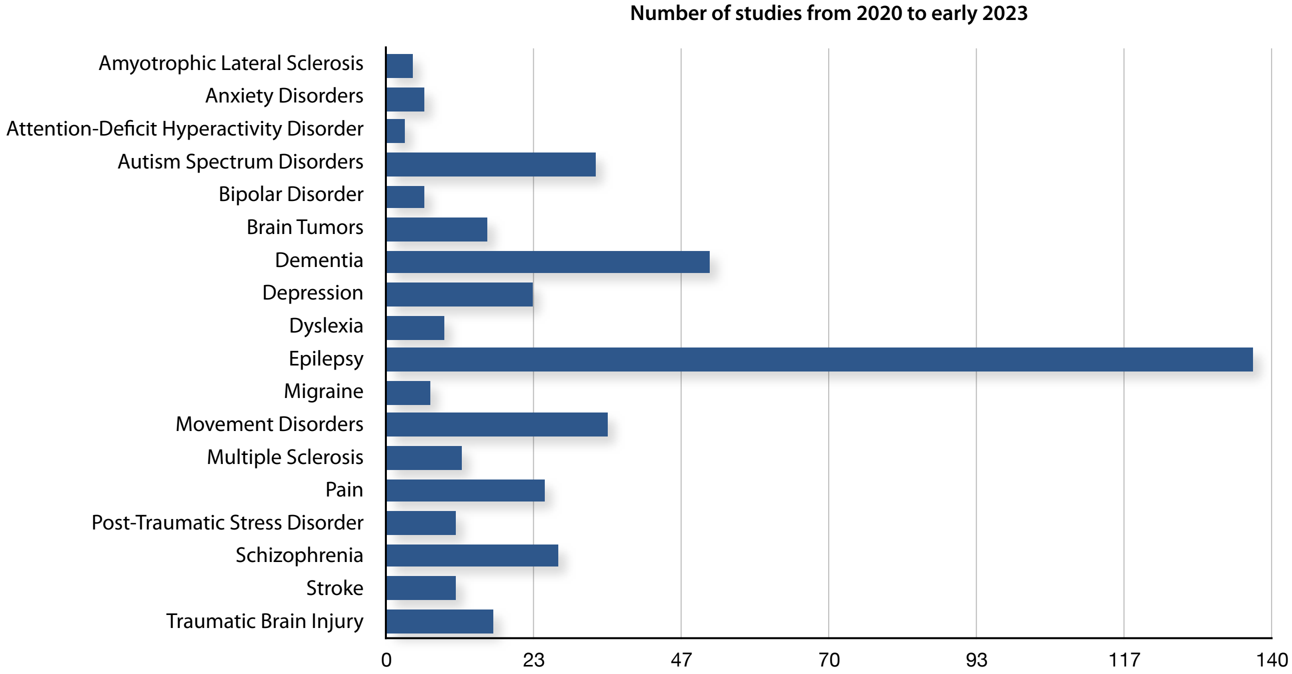
We are once again delighted about the great number and high quality of magnetoencephalography (MEG) research published every year by MEGIN customers as well as by users of other MEG devices.

While this is by no means a comprehensive bibliography of magnetoencephalography research, this book presents you with a selection of abstracts we believe reflect some of the more exciting and influential clinical research using this technology. We have not included non-clinical research in this publication due to the sheer number of studies published in such topics.

When selecting abstracts for this book, we reviewed 650 studies published from 2020 through early 2023 (this book was compiled in March 2023). These papers involved thousands and thousands of patients, spanning diseases from epilepsy, dementias, and autism spectrum disorders to brain tumors, brain injuries as well as many other topics. The below chart indicates the number of studies into some of the most studied of these disorders and conditions during the years covered by this book.

The majority of the articles we reviewed were published in prestigious peer-reviewed journals, which makes us believe that the overall quality of the research is outstanding and worth sharing with the user community as well as professionals aspring to become familiar with MEG.

While in no way complete, we hope this collection is useful to you who may want to learn about how MEG is currently used in clinical research or are perhaps interested in studies pertaining to a particular disorder. MEGIN does not, however, assume any responsibility for the content of the studies included in this book.



Amyotrophic Lateral Sclerosis

Flexibility of Fast Brain Dynamics and Disease Severity in Amyotrophic Lateral Sclerosis (2022)

Polverino, Arianna; Troisi Lopez, Emahnuel; Minino, Roberta; Liparoti, Marianna; Romano, Antonella; Trojsi, Francesca; Lucidi, Fabio; Gollo, Leonardo; Jirsa, Viktor; Sorrentino, Giuseppe; Sorrentino, Pierpaolo

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BACKGROUND AND OBJECTIVES Amyotrophic lateral sclerosis (ALS) is a multisystem disorder, as supported by clinical, molecular, and neuroimaging evidence. As a consequence, predicting clinical features requires a description of large-scale neuronal dynamics. Normally, brain activity dynamically reconfigures over time, recruiting different brain areas. Brain pathologies induce stereotyped dynamics which, in turn, are linked to clinical impairment. Hence, based on recent evidence showing that brain functional networks become hyperconnected as ALS progresses, we hypothesized that the loss of flexible dynamics in ALS would predict the symptoms severity.

METHODS To test this hypothesis, we quantified flexibility using the "functional repertoire" (i.e., the number of configurations of active brain areas) as measured from source-reconstructed magnetoencephalography (MEG) in patients with ALS and healthy controls. The activity of brain areas was reconstructed in the classic frequency bands, and the functional repertoire was estimated to quantify spatiotemporal fluctuations of brain activity. Finally, we built a k-fold cross-validated multilinear model to predict the individual clinical impairment from the size of the functional repertoire.

RESULTS Comparing 42 patients with ALS and 42 healthy controls, we found a more stereotyped brain dynamics in patients with ALS ($p < 0.05$), as conveyed by the smaller functional repertoire. The relationship between the size of the functional repertoire and the clinical scores in the ALS group showed significant correlations in both the delta and the theta frequency bands. Furthermore, through a k-fold cross-validated multilinear regression model, we found that the functional repertoire predicted both clinical staging ($p < 0.001$ and $p < 0.01$, in the delta and theta bands, respectively) and symptoms severity ($p < 0.001$, in both the delta and theta bands).

DISCUSSION Our work shows that (1) ALS pathology reduces the flexibility of large-scale brain dynamics, (2) subcortical regions play a key role in determining brain dynamics, and (3) reduced brain flexibility predicts disease stage and symptoms severity. Our approach

provides a noninvasive tool to quantify alterations in brain dynamics in ALS (and, possibly, other neurodegenerative diseases), thus opening new opportunities in disease management and a framework to test, in the near future, the effects of disease-modifying interventions at the whole-brain level.

Neurology (2022), Vol. 99, No. 21 (36180240) (0 citations)

The progressive loss of brain network fingerprints in Amyotrophic Lateral Sclerosis predicts clinical impairment (2022)

Romano, Antonella; Trosi Lopez, Emahnuel; Liparoti, Marianna; Polverino, Arianna; Minino, Roberta; Trojsi, Francesca; Bonavita, Simona; Mandolesi, Laura; Granata, Carmine; Amico, Enrico; Sorrentino, Giuseppe; Sorrentino, Pierpaolo

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ABSTRACT Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by functional connectivity alterations in both motor and extra-motor brain regions. Within the framework of network analysis, fingerprinting represents a reliable approach to assess subject-specific connectivity features within a given population (healthy or diseased). Here, we applied the Clinical Connectome Fingerprint (CCF) analysis to source-reconstructed magnetoencephalography (MEG) signals in a cohort of seventy-eight subjects: thirty-nine ALS patients and thirty-nine healthy controls. We set out to develop an identifiability matrix to assess the extent to which each patient was recognisable based on his/her connectome, as compared to healthy controls. The analysis was performed in the five canonical frequency bands. Then, we built a multilinear regression model to test the ability of the "clinical fingerprint" to predict the clinical evolution of the disease, as assessed by the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-r), the King's disease staging system, and the Milano-Torino Staging (MiToS) disease staging system. We found a drop in the identifiability of patients in the alpha band compared to the healthy controls. Furthermore, the "clinical fingerprint" was predictive of the ALSFRS-r ($p = 0.0397$; $\beta = 32.8$), the King's ($p = 0.0001$; $\beta = -7.40$), and the MiToS ($p = 0.0025$; $\beta = -4.9$) scores. Accordingly, it negatively correlated with the King's (Spearman's rho = -0.6041, $p = 0.0003$) and MiToS scales (Spearman's rho = -0.4953, $p = 0.0040$). Our results demonstrated the ability of the CCF approach to predict the individual motor impairment in patients affected by ALS. Given the subject-specificity of our approach, we hope to further exploit it to improve disease management.

Keywords: Brain network identifiability, Clinical connectome fingerprint, Functional connectome, Magnetoencephalography, Phase Linearity Measurement, Motor neurons disease, Neurodegenerative diseases

NeuroImage. Clinical (2022), Vol. 35 (35764029) (2 citations)

Cortical and subcortical changes in resting-state neuronal activity and connectivity in early symptomatic ALS and advanced frontotemporal dementia (2022)

Govaarts, Rosanne; Beeldman, Emma; Fraschini, Matteo; Griffa, Alessandra; Engels, Marjolein M A; van Es, Michael A; Veldink, Jan H; van den Berg, Leonard H; van der Kooi, Anneke J; Pijnenburg, Yolande A L; de Visser, Marianne; Stam, Cornelis J; Raaphorst, Joost; Hillebrand, Arjan

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ABSTRACT The objective of this study was to examine if patterns of resting-state brain activity and functional connectivity in cortical and subcortical regions in patients with early symptomatic amyotrophic lateral sclerosis (ALS) resemble those of behavioural variant frontotemporal dementia (bvFTD). In a cross-sectional design, eyes-closed resting-state magnetoencephalography (MEG) data of 34 ALS patients, 18 bvFTD patients and 18 age- and gender-matched healthy controls (HCs) were projected to source-space using an atlas-based beamformer. Group differences in peak frequency, band-specific oscillatory activity and functional connectivity (corrected amplitude envelope correlation) in 78 cortical regions and 12 subcortical regions were determined. False discovery rate was used to correct for multiple comparisons. BvFTD patients, as compared to ALS and HCs, showed lower relative beta power in parietal, occipital, temporal and nearly all subcortical regions. Compared to HCs, patients with ALS and patients with bvFTD had a higher delta (0.5-4 Hz) and gamma (30-48 Hz) band resting-state functional connectivity in a high number of overlapping regions in the frontal lobe and in limbic and subcortical regions. Higher delta band connectivity was widespread in the bvFTD patients compared to HCs. ALS showed a more widespread higher gamma band functional connectivity compared to bvFTD. In conclusion, MEG in early symptomatic ALS patients shows resting-state functional connectivity changes in frontal, limbic and subcortical regions that overlap considerably with bvFTD. The findings show the potential of MEG to detect brain changes in early symptomatic phases of ALS and contribute to our understanding of the disease spectrum, with ALS and bvFTD at the two extreme ends.

Keywords: Amyotrophic lateral sclerosis, Behavioural variant frontotemporal dementia, Functional connectivity, Magnetoencephalography, Oscillatory brain activity, Resting-state

NeuroImage. Clinical (2022), Vol. 34 (35217500) (0 citations)

In Amyotrophic Lateral Sclerosis Blood Cytokines Are Altered, but Do Not Correlate with Changes in Brain Topology (2020)

Polverino, Arianna; Rucco, Rosaria; Stillitano, Ilaria; Bonavita, Simona; Grimaldi, Manuela; Minino, Roberta; Pesoli, Matteo; Trojsi, Francesca; D'Ursi, Anna Maria; Sorrentino, Giuseppe; Sorrentino, Pierpaolo

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ABSTRACT Aim: The present study aims at investigating the possible correlation between peripheral markers of inflammation and brain networks. Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease dominated by progressive motor impairment. Among the complex mechanisms contributing to the pathogenesis of the disease, neuroinflammation, which is associated with altered circulating cytokine levels, is suggested to play a prominent role. Methods: Based on magnetoencephalography data, we estimated topological properties of the brain networks in ALS patients and healthy controls. Subsequently, the blood levels of a subset of cytokines were assayed. Finally, we modeled the brain topological features in the function of the cytokine levels. Results: Significant differences were found in the levels of the cytokines interleukin (IL)-4, IL-1β, and interferon-gamma (IFN-γ) between patients and controls. In particular, IL-4 and IL-1β levels increased in ALS patients, while the IFN-γ level was higher in healthy controls. We also detected modifications in brain global topological parameters in terms of hyperconnectedness. Despite both blood cytokines and brain topology being altered in ALS patients, such changes do not appear to be in a direct relationship. Conclusion: Our results would be in line with the idea that topological changes relate to neurodegenerative processes. However, the absence of correlation between blood cytokines and topological parameters of brain networks does not preclude that inflammatory processes contribute to the alterations of the brain networks. Impact statement The progression of amyotrophic lateral sclerosis entails both neurodegenerative and inflammatory processes. Furthermore, disease progression induces global modifications of the brain networks, with advanced stages showing a more compact, hyperconnected network topology. The pathophysiological processes underlying topological changes are unknown. In this article, we hypothesized that the global inflammatory profile would relate to the topological alterations. Our results showed that this is not the case, as modeling the topological properties as a function of the inflammatory state did not yield good predictions. Hence, our results suggest that topological changes might directly relate to neurodegenerative processes instead.

Keywords: amyotrophic lateral sclerosis, brain networks, connectivity, cytokines, magnetoencephalography, neuroinflammation

Brain connectivity (2020), Vol. 10, No. 8 (32731760) (7 citations)

Anxiety Disorders

Preliminary Observations of Resting-State Magnetoencephalography in Nonmedicated Children with Obsessive-Compulsive Disorder (2022)

Tan, Vinh; Dockstader, Colleen; Moxon-Emre, Iska; Mendlowitz, Sandra; Schacter, Reva; Colasanto, Marlena; Voineskos, Aristotle N; Akingbade, Aquila; Nishat, Eman; Mabbott, Donald J; Arnold, Paul D; Ameis, Stephanie H

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ABSTRACT Background: Cortico-striato-thalamo-cortical (CSTC) network alterations are hypothesized to contribute to symptoms of obsessive-compulsive disorder (OCD). To date, very few studies have examined whether CSTC network alterations are present in children with OCD, who are medication naive. Medication-naive pediatric imaging samples may be optimal to study neural correlates of illness and identify brain-based markers, given the proximity to illness onset. Methods: Magnetoencephalography (MEG) data were analyzed at rest, in 18 medication-naive children with OCD (M = 12.1 years ±2.0 standard deviation [SD]; 10 M/8 F) and 13 typically developing children (M = 12.3 years ±2.2 SD; 6 M/7 F). Whole-brain MEG-derived resting-state functional connectivity (rs-fc), for alpha- and gamma-band frequencies were compared between OCD and typically developing (control) groups. Results: Increased MEG-derived rs-fc across alpha- and gamma-band frequencies was found in the OCD group compared to the control group. Increased MEG-derived rs-fc at alpha-band frequencies was evident across a number of regions within the CSTC circuitry and beyond, including the cerebellum and limbic regions. Increased MEG-derived rs-fc at gamma-band frequencies was restricted to the frontal and temporal cortices. Conclusions: This MEG study provides preliminary evidence of altered alpha and gamma networks, at rest, in medication-naive children with OCD. These results support prior findings pointing to the relevance of CSTC circuitry in pediatric OCD and further support accumulating evidence of altered connectivity between regions that extend beyond this network, including the cerebellum and limbic regions. Given the substantial portion of children and youth whose OCD symptoms do not respond to conventional treatments, our findings have implications for future treatment innovation research aiming to target and track whether brain patterns associated with having OCD may change with treatment and/or predict treatment response.

Keywords: MEG, OCD, brain oscillations, frequency bands, magnetoencephalography, medication naive, obsessive-compulsive disorder, pediatric, resting-state functional connectivity, rs-fc

Journal of child and adolescent psychopharmacology (2022), Vol. 32, No. 10 (36548364) (0 citations)

Neural correlates of fear conditioning are associated with treatment-outcomes to behavioral exposure in spider phobia - Evidence from magnetoencephalography (2022)

Roesmann, Kati; Toelle, Julius; Leehr, Elisabeth Johanna; Wessing, Ida; Böhnlein, Joscha; Seeger, Fabian; Schwarzmeier, Hanna; Siminski, Niklas; Herrmann, Martin J; Dannlowski, Udo; Lueken, Ulrike; Klucken, Tim; Straube, Thomas; Junghöfer, Markus

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BACKGROUND Models of anxiety disorders and the rationale of exposure therapy (ET) are grounded on classical fear conditioning. Yet, it is unclear whether lower fear ratings of conditioned safety versus threat cues and corresponding neural markers of safety-learning and/or fear inhibition assessed before treatment would predict better outcomes of behavioral exposure.

METHODS Sixty-six patients with spider phobia completed pre-treatment clinical and experimental fear conditioning assessments, one session of virtual reality ET, a post-treatment clinical assessment, and a 6-month follow-up assessment. Tilted Gabor gratings served as conditioned stimuli (CS) that were either paired (CS+) or remained unpaired (CS-) with an aversive phobia-related and phobia-unrelated unconditioned stimulus (UCS). CS+/CS- differences in fear ratings and magnetoencephalographic event-related fields (ERFs) were related to percentual symptom reductions from pre- to post-treatment, as assessed via spider phobia questionnaire (SPQ), behavioral avoidance test (BAT), and remission status at 6-month follow-up.

RESULTS We observed no associations between pre-treatment CS+/CS- differences in fear ratings and any treatment outcome. CS+/CS- differences in source estimations of ERFs revealed that higher CS- activity in bilateral dorsolateral prefrontal cortex (dlPFC) was related with SPQ- and BAT-reductions. Associations between CS+/CS- differences and treatment outcomes were also observed in left ventromedial prefrontal cortex (vmPFC) regions, which additionally revealed associations with the follow-up remission status.

CONCLUSIONS Results provide initial evidence that neural pre-treatment CS+/CS- differences may hold predictive information regarding outcomes of behavioral exposure. Our findings highlight a key role of neural responses to safety cues with potentially inhibitory effects on affect-generating structures during fear conditioning.

Keywords: Anxiety disorders, Exposure outcome, Fear conditioning, MEG/EEG, Specific phobia, Virtual reality exposure therapy

NeuroImage. Clinical (2022), Vol. 35 (35609411) (1 citation)

Behavioral and Magnetoencephalographic Correlates of Fear Generalization Are Associated With Responses to Later Virtual Reality Exposure Therapy in Spider Phobia (2022)

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BACKGROUND Because overgeneralization of fear is a pathogenic marker of anxiety disorders, we investigated whether pretreatment levels of fear generalization in spider-phobic patients are related to their response to exposure-based treatment to identify pretreatment moderators of treatment success.

METHODS A total of 90 patients with spider phobia completed pretreatment clinical and magnetoencephalography assessments, one session of virtual reality exposure therapy, and a posttreatment clinical assessment. Based on the primary outcome (30% symptom reduction in self-reported symptoms), they were categorized as responders or nonresponders. In a pretreatment magnetoencephalography fear generalization paradigm involving fear conditioning with 2 unconditioned stimuli (UCS), we obtained fear ratings, UCS expectancy ratings, and event-related fields to conditioned stimuli (CS: CS-, CS+) and 7 different generalization stimuli on a perceptual continuum from CS- to CS+.

RESULTS Before treatment, nonresponders showed behavioral overgeneralization indicated by more linear generalization gradients in fear ratings. Analyses of magnetoencephalography source estimations revealed that nonresponders showed a decline of their (inhibitory) frontal activations to safety-signaling CS- and generalization stimuli compared with CS+ over time, while responders maintained these activations at early (<300 ms) and late processing stages.

CONCLUSIONS Results provide initial evidence that pretreatment differences of behavioral and neural markers of fear generalization may act as moderators of later responses to behavioral exposure. Stimulating further research on fear generalization as a potential predictive marker, our findings are an important first step in the attempt to identify patients who may not benefit from exposure therapy and to personalize and optimize treatment strategies for this vulnerable patient group.

Keywords: Anxiety disorders, Exposure outcome, Fear generalization, MEG/EEG, Specific phobia, Virtual reality exposure therapy

Biological psychiatry. Cognitive neuroscience and neuroimaging (2022), Vol. 7, No. 2 (34325047) (3 citations)

Reduced coupling of somatosensory gating and gamma oscillation in panic disorder (2021)

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ABSTRACT Previous studies have reported that patients with panic disorder (PD) exhibited an aberrant level of GABA concentration, an inhibitory neurotransmitter in the human brain. However, it remains substantially unclear whether the inhibitory function regarding the neurophysiological characteristics is altered in this disease. Sensory gating (SG) is considered as an automatic inhibitory function in the sensory cortex. In addition, brain's gamma oscillation within the sensory cortex is another index to reflect inhibitory function. Here we aimed to investigate whether the patients with PD showed altered inhibitory function in the somatosensory system, including the primary (SI) and secondary (SII) somatosensory cortices. A total of 20 healthy controls and 21 patients with PD underwent magnetoencephalographic recordings. Paired-pulse and single-pulse paradigms were used to study SG and gamma oscillations, respectively. There were no significant between-group differences in the SG function in the SI and SII. However, patients with PD demonstrated a reduced gamma power in the SI. Among the healthy individuals, strong associations between SG ratios and gamma frequency values were observed in the SI. However, such a functional relationship disappeared among the patients with PD. We suggested the reduced coupling of SG and gamma oscillation as one of the neural signatures in PD.

Keywords: Gamma oscillation, Inhibitory function, Magnetoencephalography (MEG), Primary somatosensory cortex (SI), Sensory gating

Psychiatry research. Neuroimaging (2021), Vol. 307 (33248324) (0 citations)

Dysfunctional frontal activation of mismatch negativity in panic disorder: A magnetoencephalographic study (2021)

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BACKGROUND Mismatch negativity (MMN) or its magnetic counterpart (MMNm) is a neurophysiological signal to reflect the automatic change-detection ability. However, MMN studies in patients with panic disorder (PD) showed contrasting results using electroencephalographic (EEG) recordings. The present study attempted to overcome the limitations of EEG methodology by means of a whole-head magnetoencephalography (MEG) combined with the depth-weighted minimum norm estimate method to conduct an in-depth investigation on the MMNm at the cortical level in patients with PD.

METHODS We recruited 22 healthy controls (HC) and 20 patients with PD to perform auditory oddball paradigm during MEG recordings. The cortical MMNm amplitudes and latencies in the superior temporal gyrus, inferior parietal lobule, and inferior frontal gyrus (IFG) were compared between the HC and PD groups. The correlations between MMNm responses and clinical measurement were also examined.

RESULTS Compared with the HC group, the PD group demonstrated significantly reduced MMNm amplitudes in the IFG. Furthermore, higher trait scores of the State-Trait Anxiety Inventory were associated with lower MMNm amplitudes of the right IFG among patients with PD.

LIMITATIONS Generalization of the current results to other settings or samples should be made cautiously due to the use of different medication regimens and presence of comorbidities in our patients.

CONCLUSIONS Our data suggest dysfunctional pre-attentive change-detection ability in patients with PD, particularly in the IFG.

Keywords: Inferior frontal gyrus (IFG), Magnetoencephalography (MEG), Mismatch negativity (MMN), Panic disorder (PD)

Journal of affective disorders (2021), Vol. 280, No. Pt A (33220556) (0 citations)

Cumulative Risk on Oxytocin-Pathway Genes Impairs Default Mode Network Connectivity in Trauma-Exposed Youth (2020)

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ABSTRACT Background: Although the default mode network (DMN) is a core network essential for brain functioning, little is known about its developmental trajectory, particularly on factors associated with its coherence into a functional network. In light of adult studies indicating DMN's susceptibility to stress-related conditions, we examined links between variability on oxytocin-pathway genes and DMN connectivity in youth exposed to chronic war-related trauma Methods: Following a cohort of war-exposed children from early childhood, we imaged the brains of 74 preadolescents (age 11-13 years; 39 war-exposed) during rest using magnetoencephalography (MEG). A cumulative risk index on oxytocin-pathway genes was constructed by combining single nucleotide polymorphisms on five genes previously linked with social deficits and psychopathology; OXTR rs1042778, OXTR rs2254298, OXTRrs53576, CD38 rs3796863, and AVPR1A RS3. Avoidant response to trauma reminders in early childhood and anxiety disorders in late childhood were assessed as predictors of disruptions to DMN theta connectivity. Results: Higher vulnerability on oxytocin-pathway genes predicted greater disruptions to DMN theta connectivity. Avoidant symptoms in early childhood and generalized anxiety disorder in later childhood were related to impaired DMN connectivity. In combination, stress exposure, oxytocin-pathway genes, and stress-related symptoms explained 24.6% of the variance in DMN connectivity, highlighting the significant effect of stress on the maturing brain. Conclusions: Findings are the first to link the oxytocin system and maturation of the DMN, a core system sustaining autobiographical memories, alteration of intrinsic and extrinsic attention, mentalization, and sense of self. Results suggest that oxytocin may buffer the effects of chronic early stress on the DMN, particularly theta rhythms that typify the developing brain.

Keywords: OXTR, anxiety disorders, genetics, longitudinal studies, magnetoencephalography, trauma exposure

Frontiers in endocrinology (2020), Vol. 11 (32528417) (0 citations)

Attention-Deficit Hyperactivity Disorder

Electrophysiological Brain Changes Associated With Cognitive Improvement in a Pediatric Attention Deficit Hyperactivity Disorder Digital Artificial Intelligence-Driven Intervention: Randomized Controlled Trial (2021)

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BACKGROUND Cognitive stimulation therapy appears to show promising results in the rehabilitation of impaired cognitive processes in attention deficit hyperactivity disorder.

OBJECTIVE Encouraged by this evidence and the ever-increasing use of technology and artificial intelligence for therapeutic purposes, we examined whether cognitive stimulation therapy implemented on a mobile device and controlled by an artificial intelligence engine can be effective in the neurocognitive rehabilitation of these patients.

METHODS In this randomized study, 29 child participants (25 males) underwent training with a smart, digital, cognitive stimulation program (KAD_SCL_01) or with 3 commercial video games for 12 weeks, 3 days a week, 15 minutes a day. Participants completed a neuropsychological assessment and a preintervention and postintervention magnetoencephalography study in a resting state with their eyes closed. In addition, information on clinical symptoms was collected from the child´s legal guardians.

RESULTS In line with our main hypothesis, we found evidence that smart, digital, cognitive treatment results in improvements in inhibitory control performance. Improvements were also found in visuospatial working memory performance and in the cognitive flexibility, working memory, and behavior and general executive functioning behavioral clinical indexes in this group of participants. Finally, the improvements found in inhibitory control were related to increases in alpha-band power in all participants in the posterior regions, including 2 default mode network regions of the interest: the bilateral precuneus and the bilateral posterior cingulate cortex. However, only the participants who underwent cognitive stimulation intervention (KAD_SCL_01) showed a significant increase in this relationship.

CONCLUSIONS The results seem to indicate that smart, digital treatment can be effective in the inhibitory control and visuospatial working memory rehabilitation in patients with attention deficit hyperactivity disorder. Furthermore, the relation of the inhibitory control with alpha-band power changes could mean that these changes are a product of plasticity mechanisms or changes in the neuromodulatory dynamics.

TRIAL REGISTRATION ISRCTN Registry ISRCTN71041318; https://www.isrctn.com/ISRCTN71041318.

Keywords: ADHD, AI, Conners continuous performance test, KAD_SCL_01, artificial intelligence, attention deficit hyperactivity disorder, children, cognitive impairment, cognitive stimulation, magnetoencephalography, pediatrics, rehabilitation

Journal of medical Internet research (2021), Vol. 23, No. 11 (34842533) (4 citations)

High-gamma oscillations as neurocorrelates of ADHD: A MEG crossover placebo-controlled study (2021)

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ABSTRACT Attention Deficit Hyperactive Disorder (ADHD) is a common neurobehavioral disorder with a significant and pervasive impact on patients' lives. Identifying neurophysiological correlates of ADHD is important for understanding its underlying mechanisms, as well as for improving clinical accuracy beyond cognitive and emotional factors. The present study focuses on finding a diagnostic stable neural correlate based on evaluating MEG resting state frequency bands. Twenty-two ADHD patients and 23 controls adults were blindly randomized to two methylphenidate/placebo evaluation days. On each evaluation day state anxiety was assessed, a 2N-back executive function task was performed, and resting state MEG brain activity was recorded at three timepoints. A frequency-based cluster analysis yielded higher high-gamma power for ADHD over posterior sensors and lower high-gamma power for ADHD over frontal-central sensors. These results were shown to be stable over three measurements, unaffected by methylphenidate treatment, and linked to cognitive accuracy and state anxiety. Furthermore, the differential high-gamma activity evidenced substantial ADHD diagnostic efficacy, comparable to the cognitive and emotional factors. These results indicate that resting state high-gamma activity is a promising, stable, valid and diagnostically-relevant neurocorrelate of ADHD. Due to the evolving understanding both in the cellular and network level of high-gamma oscillations, focusing future studies on this frequency band bears the potential for a better understanding of ADHD, thus advancing the specificity of the evaluation of the disorder and developing new tools for therapy.

Keywords: ADHD, High gamma, Magnetoencephalography, Methylphenidate, N-back, State anxiety

Journal of psychiatric research (2021), Vol. 137 (33684643) (1 citation)

Characterizing Inscapes and resting-state in MEG: Effects in typical and atypical development (2021)

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ABSTRACT Examining the brain at rest is a powerful approach used to understand the intrinsic properties of typical and disordered human brain function, yet task-free paradigms are associated with greater head motion, particularly in young and/or clinical populations such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Inscapes, a non-social and non-verbal movie paradigm, has been introduced to increase attention, thus mitigating head motion, while reducing the task-induced activations found during typical movie watching. Inscapes has not yet been validated for use in magnetoencephalography (MEG), and it has yet to be shown whether its effects are stable in clinical populations. Across typically developing (N = 32) children and adolescents and those with ASD (N = 46) and ADHD (N = 42), we demonstrate that head motion is reduced during Inscapes. Due to the task state evoked by movie paradigms, we also expectedly observed concomitant modulations in local neural activity (oscillatory power) and functional connectivity (phase and envelope coupling) in intrinsic resting-state networks and across the frequency spectra compared to a fixation cross resting-state. Increases in local activity were accompanied by decreases in low-frequency connectivity within and between resting-state networks, primarily the visual network, suggesting that task-state evoked by Inscapes moderates ongoing and spontaneous cortical inhibition that forms the idling intrinsic networks found during a fixation cross resting-state. Importantly, these effects were similar in ASD and ADHD, making Inscapes a well-suited advancement for investigations of resting brain function in young and clinical populations.

Keywords: Attention-deficit/hyperactivity disorder, Autism spectrum disorder, Inscapes, Magnetoencephalography, Neurodevelopmental disorders, Resting-state

NeuroImage (2021), Vol. 225 (33147510) (4 citations)

Autism Spectrum Disorders

Gamma oscillations point to the role of primary visual cortex in atypical motion processing in autism (2023)

Orekhova, Elena V; Manyukhina, Viktoriya O; Galuta, Ilia A; Prokofyev, Andrey O; Goiaeva, Dzerassa E; Obukhova, Tatiana S; Fadeev, Kirill A; Schneiderman, Justin F; Stroganova, Tatiana A

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ABSTRACT Neurophysiological studies suggest that abnormal neural inhibition may explain a range of sensory processing differences in autism spectrum disorders (ASD). In particular, the impaired ability of people with ASD to visually discriminate the motion direction of small-size objects and their reduced perceptual suppression of background-like visual motion may stem from deficient surround inhibition within the primary visual cortex (V1) and/or its atypical top-down modulation by higher-tier cortical areas. In this study, we estimate the contribution of abnormal surround inhibition to the motion-processing deficit in ASD. For this purpose, we used a putative correlate of surround inhibition-suppression of the magnetoencephalographic (MEG) gamma response (GR) caused by an increase in the drift rate of a large annular high-contrast grating. The motion direction discrimination thresholds for the gratings of different angular sizes (1° and 12°) were assessed in a separate psychophysical paradigm. The MEG data were collected in 42 boys with ASD and 37 typically developing (TD) boys aged 7-15 years. Psychophysical data were available in 33 and 34 of these participants, respectively. The results showed that the GR suppression in V1 was reduced in boys with ASD, while their ability to detect the direction of motion was compromised only in the case of small stimuli. In TD boys, the GR suppression directly correlated with perceptual suppression caused by increasing stimulus size, thus suggesting the role of the top-down modulations of V1 in surround inhibition. In ASD, weaker GR suppression was associated with the poor directional sensitivity to small stimuli, but not with perceptual suppression. These results strongly suggest that a local inhibitory deficit in V1 plays an important role in the reduction of directional sensitivity in ASD and that this perceptual deficit cannot be explained exclusively by atypical top-down modulation of V1 by higher-tier cortical areas.

PloS one (2023), Vol. 18, No. 2 (36780507) (0 citations)

Machine learning approaches for electroencephalography and magnetoencephalography analyses in autism spectrum disorder: A systematic review (2023)

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ABSTRACT There are growing application of machine learning models to study the intricacies of non-linear and non-stationary characteristics of electroencephalography (EEG) and magnetoencephalography (MEG) data in neurobiologically complex and heterogeneous conditions such as autism spectrum disorder (ASD). Such tools have potential diagnostic applications, and given the highly heterogeneous presentation of ASD, might prove fruitful in early detection and therefore could facilitate very early intervention. We conducted a systematic review (PROSPERO ID#CRD42021257438) by searching PubMed, EMBASE, and PsychINFO for machine learning approaches for EEG and MEG analyses in ASD. Thirty-nine studies were identified, of which the majority (18) used support vector machines for classification; other successful methods included deep learning. Thirty-seven studies were found to employ EEG and two were found to employ MEG. This systematic review indicate that machine learning methods can be used to classify ASD, predict ASD diagnosis in high-risk infants as early as 3 months of age, predict ASD symptom severity, and classify states of cognition in ASD with high accuracy. Replication studies testing validity, reproducibility and generalizability in tandem with randomized controlled trials in ASD populations will likely benefit the field.

Keywords: Autism, Electroencephalography, Machine learning, Magnetoencephalography, Neurophysiology, Review, Support vector machines, Systematic

Progress in neuro-psychopharmacology & biological psychiatry (2023), Vol. 123 (36574922) (0 citations)

Neuromagnetic 40 Hz Auditory Steady-State Response in the left auditory cortex is related to language comprehension in children with Autism Spectrum Disorder (2023)

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ABSTRACT Language impairment is comorbid in most children with Autism Spectrum Disorder (ASD), but its neural mechanisms are still poorly understood. Some studies hypothesize that the atypical low-level sensory perception in the auditory cortex accounts for the abnormal language development in these children. One of the potential non-invasive measures of such low-level perception can be the cortical gamma-band oscillations registered with magnetoencephalography (MEG), and 40 Hz Auditory Steady-State Response (40 Hz ASSR) is a reliable paradigm for eliciting auditory gamma response. Although there is research in children with and without ASD using 40 Hz ASSR, nothing is known about the relationship between this auditory response in children with ASD and their language

abilities measured directly in formal assessment. In the present study, we used MEG and individual brain models to investigate 40 Hz ASSR in primary-school-aged children with and without ASD. It was also used to assess how the strength of the auditory response is related to language abilities of children with ASD, their non-verbal IQ, and social functioning. A total of 40 children were included in the study. The results demonstrated that 40 Hz ASSR was reduced in the right auditory cortex in children with ASD when comparing them to typically developing controls. Importantly, our study provides the first evidence of the association between 40 Hz ASSR in the language-dominant left auditory cortex and language comprehension in children with ASD. This link was domain-specific because the other brain-behavior correlations were non-significant.

Keywords: 40Hz Auditory Steady-State Response (40Hz ASSR), Amplitude-modulated tones, Auditory gamma oscillations, Autism Spectrum Disorder (ASD), Magnetoencephalography (MEG)

Progress in neuro-psychopharmacology & biological psychiatry (2023), Vol. 122 (36470421) (0 citations)

The dual neural effects of oxytocin in autistic youth: results from a randomized trial (2022)

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ABSTRACT Recent discoveries have highlighted the effects of oxytocin (OT) on social behavior and perception among autistic individuals. However, a gap persists in the literature regarding the potential effects of OT and the neural temporal dynamics due to OT administration. We explored the effect of OT on autistic individuals using magnetoencephalography (MEG), focusing on M100, M170, and M250, social perception-related components that tend to show atypical patterns in autistic individuals. Twenty-five autistic adolescents participated in this randomized, double-blind MEG study. Autistic individuals arrived at the lab twice and received an acute dose of intranasal OT or placebo in each session. During the scans, participants were asked to identify pictures of social and non-social stimuli. Additionally, 23 typically developing (TD) adolescents performed the same task in the MEG as a benchmark that allowed us to better characterize neural regions of interest and behavioral results for this age group in this task. A source-model beamformer analysis revealed that OT enhanced neural activity for social stimuli in frontal regions during M170. Additionally, in each of the preselected time windows, OT increased activation in the left hemisphere, regardless of the content of the presented stimuli. We suggest that OT increased the processing of social stimuli through two separate mechanisms. First, OT increased neural activity in a nonspecific manner, allowing increased allocation of attention toward the stimuli. Second, OT enhanced M170 activity in frontal regions only in response to social stimuli. These results reveal the temporal dynamics of the effects of OT on the early stages of social and non-social perception in autistic adolescents.Trial registration: This study was a part of a project registered as clinical trial October 27th, 2021. ClinicalTrials.gov Identifier: NCT05096676.

Scientific reports (2022), Vol. 12, No. 1 (36175473) (0 citations)

Globally elevated excitation-inhibition ratio in children with autism spectrum disorder and below-average intelligence (2022)

Manyukhina, Viktoriya O; Prokofyev, Andrey O; Galuta, Ilia A; Goiaeva, Dzerassa E; Obukhova, Tatiana S; Schneiderman, Justin F; Altukhov, Dmitrii I; Stroganova, Tatiana A; Orekhova, Elena V

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BACKGROUND Altered neuronal excitation-inhibition (E-I) balance is strongly implicated in ASD. However, it is not known whether the direction and degree of changes in the E-I ratio in individuals with ASD correlates with intellectual disability often associated with this developmental disorder. The spectral slope of the aperiodic 1/f activity reflects the E-I balance at the scale of large neuronal populations and may uncover its putative alternations in individuals with ASD with and without intellectual disability.

METHODS Herein, we used magnetoencephalography (MEG) to test whether the 1/f slope would differentiate ASD children with average and below-average (< 85) IQ. MEG was recorded at rest with eyes open/closed in 49 boys with ASD aged 6-15 years with IQ ranging from 54 to 128, and in 49 age-matched typically developing (TD) boys. The cortical source activity was estimated using the beamformer approach and individual brain models. We then extracted the 1/f slope by fitting a linear function to the log-log-scale power spectra in the high-frequency range.

RESULTS The global 1/f slope averaged over all cortical sources demonstrated high rank-order stability between the two conditions. Consistent with previous research, it was steeper in the eyes-closed than in the eyes-open condition and flattened with age. Regardless of condition, children with ASD and below-average IQ had flatter slopes than either TD or ASD children with average or above-average IQ. These group differences could not be explained by differences in signal-to-noise ratio or periodic (alpha and beta) activity.

LIMITATIONS Further research is needed to find out whether the observed changes in E-I ratios are characteristic of children with below-average IQ of other diagnostic groups.

CONCLUSIONS The atypically flattened spectral slope of aperiodic activity in children with ASD and below-average IQ suggests a shift of the global E-I balance toward hyper-excitation. The spectral slope can provide an accessible noninvasive biomarker of the E-I ratio for making objective judgments about treatment effectiveness in people with ASD and comorbid intellectual disability.

Keywords: 1/f power law, Autism spectrum disorders (ASDs), Biomarkers, Excitation–inhibition balance, Intelligence, Magnetoencephalography, Power spectrum

Molecular autism (2022), Vol. 13, No. 1 (35550191) (2 citations)

Cortical signatures of auditory object binding in children with autism spectrum disorder are anomalous in concordance with behavior and diagnosis (2022)

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ABSTRACT Organizing sensory information into coherent perceptual objects is fundamental to everyday perception and communication. In the visual domain, indirect evidence from cortical responses suggests that children with autism spectrum disorder (ASD) have anomalous figure-ground segregation. While auditory processing abnormalities are common in ASD, especially in environments with multiple sound sources, to date, the question of scene segregation in ASD has not been directly investigated in audition. Using magnetoencephalography, we measured cortical responses to unattended (passively experienced) auditory stimuli while parametrically manipulating the degree of temporal coherence that facilitates auditory figure-ground segregation. Results from 21 children with ASD (aged 7-17 years) and 26 age- and IQ-matched typically developing children provide evidence that children with ASD show anomalous growth of cortical neural responses with increasing temporal coherence of the auditory figure. The documented neurophysiological abnormalities did not depend on age, and were reflected both in the response evoked by changes in temporal coherence of the auditory scene and in the associated induced gamma rhythms. Furthermore, the individual neural measures were predictive of diagnosis (83% accuracy) and also correlated with behavioral measures of ASD severity and auditory processing abnormalities. These findings offer new insight into the neural mechanisms underlying auditory perceptual deficits and sensory overload in ASD, and suggest that temporal-coherence-based auditory scene analysis and suprathreshold processing of coherent auditory objects may be atypical in ASD.

PLoS biology (2022), Vol. 20, No. 2 (35167585) (1 citation)

Abnormal cortical responses elicited by audiovisual movies in patients with autism spectrum disorder with atypical sensory behavior: A magnetoencephalographic study (2022)

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BACKGROUND Atypical sensory behavior disrupts behavioral adaptation in children with autism spectrum disorder (ASD); however, neural correlates of sensory dysfunction using magnetoencephalography (MEG) remain unclear.

METHOD We used MEG to measure the cortical activation elicited by visual (uni)/audiovisual (multisensory) movies in 46 children (7-14 years) were included in final analysis: 13 boys with atypical audiovisual behavior in ASD (AAV+), 10 without this condition, and 23 age-matched typically developing boys.

RESULTS The AAV+ group demonstrated an increase in the cortical activation in the bilateral insula in response to unisensory movies and in the left occipital, right superior temporal sulcus (rSTS), and temporal regions to multisensory movies. These increased responses were correlated with severity of the sensory impairment. Increased theta-low gamma oscillations were observed in the rSTS in AAV+.

CONCLUSION The findings suggest that AAV is attributed to atypical neural networks centered on the rSTS.

Keywords: Atypical audiovisual behavior, Audiovisual movies, Autism spectrum disorders, Magnetoencephalography, Sensory processing

Brain & development (2022), Vol. 44, No. 2 (34563417) (0 citations)

Biomarkers for autism spectrum disorder: opportunities for magnetoencephalography (MEG) (2021)

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ABSTRACT This paper reviews a candidate biomarker for ASD, the M50 auditory evoked response component, detected by magnetoencephalography (MEG) and presents a position on the roles and opportunities for such a biomarker, as well as converging evidence from allied imaging techniques (magnetic resonance imaging, MRI and spectroscopy, MRS). Data is presented on prolonged M50 latencies in ASD as well as extension to include children with ASD with significant language and cognitive impairments in whom M50 latency delays are exacerbated. Modeling of the M50 latency by consideration of the properties of auditory pathway white matter is shown to be successful in typical development but challenged by heterogeneity in ASD; this, however, is capitalized upon to identify a distinct subpopulation of children with ASD whose M50 latencies lie well outside the range of values predictable from the typically developing model. Interestingly, this subpopulation is characterized by low levels of the inhibitory neurotransmitter GABA. Following from this, we discuss a potential use of the M50 latency in indicating "target engagement" acutely with administration of a GABA-B agonist, potentially distinguishing "responders" from "non-responders" with the implication of optimizing inclusion for clinical trials of such agents. Implications for future application, including potential evaluation of infants with genetic risk factors, are discussed. As such, the broad scope of potential of a representative candidate biological marker, the M50 latency, is introduced along with potential future applications.This paper outlines a strategy for understanding brain dysfunction in individuals with intellectual and developmental disabilities (IDD). It is proposed that a multimodal approach (collection of brain structure, chemistry, and neuronal functional data) will identify IDD subpopulations who share a common disease pathway, and thus identify individuals with IDD who might ultimately benefit from specific treatments. After briefly demonstrating the need and potential for scope, examples from studies examining brain function and structure in children with autism spectrum disorder (ASD) illustrate how measures of brain neuronal function (from magnetoencephalography, MEG), brain structure (from magnetic resonance imaging, MRI, especially diffusion MRI), and brain chemistry (MR spectroscopy) can help us better understand the heterogeneity in ASD and form the basis of multivariate biological markers (biomarkers) useable to define clinical subpopulations. Similar approaches can be applied to understand brain dysfunction in neurodevelopmental disorders (NDD) in general. In large part, this paper represents our endeavors as part of the CHOP/Penn NICHD-funded intellectual and developmental disabilities research center (IDDRC) over the past decade.

Journal of neurodevelopmental disorders (2021), Vol. 13, No. 1 (34525943) (0 citations)

Atypical development of emotional face processing networks in autism spectrum disorder from childhood through to adulthood (2021)

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ABSTRACT Impairments in social functioning are hallmarks of autism spectrum disorder (ASD) and atypical functional connectivity may underlie these difficulties. Emotion processing networks typically undergo protracted maturational changes, however, those with ASD show either hyper- or hypo-connectivity with little consensus on the functional connectivity underpinning emotion processing. Magnetoencephalography was used to investigate age-related changes in whole-brain functional connectivity of eight regions of interest during happy and angry face processing in 190 children, adolescents and adults (6-39 years) with and without ASD. Findings revealed age-related changes from child- through to mid-adulthood in functional connectivity in controls and in ASD in theta, as well as age-related between-group differences across emotions, with connectivity decreasing in ASD, but increasing for controls, in gamma. Greater connectivity to angry faces was observed across groups in gamma. Emotion-specific age-related between-group differences in beta were also found, that showed opposite trends with age for happy and angry in ASD. Our results establish altered, frequency-specific developmental trajectories of functional connectivity in ASD, across distributed networks and a broad age range, which may finally help explain the heterogeneity in the literature.

Keywords: ASD, Age-related changes, Development, Emotional face processing, Functional connectivity, Magnetoencephalography

Developmental cognitive neuroscience (2021), Vol. 51 (34416703) (0 citations)

Visual gamma oscillations predict sensory sensitivity in females as they do in males (2021)

Manyukhina, Viktoriya O; Rostovtseva, Ekaterina N; Prokofyev, Andrey O; Obukhova, Tatiana S; Schneiderman, Justin F; Stroganova, Tatiana A; Orekhova, Elena V

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ABSTRACT Gamma oscillations are driven by local cortical excitatory (E)-inhibitory (I) loops and may help to characterize neural processing involving excitatory-inhibitory interactions. In the visual cortex reliable gamma oscillations can be recorded with magnetoencephalography (MEG) in the majority of individuals, which makes visual gamma an attractive candidate for biomarkers of brain disorders associated with E/I imbalance. Little is known, however, about if/how these oscillations reflect individual differences in neural excitability and associated sensory/perceptual phenomena. The power of visual gamma response (GR) changes nonlinearly with increasing stimulation intensity: it increases with transition from static to slowly drifting high-contrast grating and then attenuates with further increase in the drift rate. In a recent MEG study we found that the GR attenuation predicted sensitivity to sensory stimuli in everyday life in neurotypical adult men and in men with autism spectrum disorders. Here, we replicated these results in neurotypical female participants. The GR enhancement with transition from static to slowly drifting grating did not correlate significantly with the sensory sensitivity measures. These findings suggest that weak velocity-related attenuation of the GR is a reliable neural concomitant of visual hypersensitivity and that the degree of GR attenuation may provide useful information about E/I balance in the visual cortex.

Scientific reports (2021), Vol. 11, No. 1 (34103578) (0 citations)

Altered maturation and atypical cortical processing of spoken sentences in autism spectrum disorder (2021)

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ABSTRACT Autism spectrum disorder (ASD) is associated with widespread receptive language impairments, yet the neural mechanisms underlying these deficits are poorly understood. Neuroimaging has shown that processing of socially-relevant sounds, including speech and non-speech, is atypical in ASD. However, it is unclear how the presence of lexical-semantic meaning affects speech processing in ASD. Here, we recorded magnetoencephalography data from individuals with ASD (N = 22, ages 7-17, 4 females) and typically developing (TD) peers (N = 30, ages 7-17, 5 females) during unattended listening to meaningful auditory speech sentences and meaningless jabberwocky sentences. After adjusting for age, ASD individuals showed stronger responses to meaningless jabberwocky sentences than to meaningful speech sentences in the same left temporal and parietal language regions where TD individuals exhibited stronger responses to meaningful speech. Maturational trajectories of meaningful speech responses were atypical in temporal, but not parietal, regions in ASD. Temporal responses were associated with ASD severity, while parietal responses were associated with aberrant involuntary attentional shifting in ASD. Our findings suggest a receptive speech processing dysfunction in ASD, wherein unattended meaningful speech elicits abnormal engagement of the language system, while unattended meaningless speech, filtered out in TD individuals, engages the language system through involuntary attention capture.

Keywords: Auditory, Autism, Event-related fields, Language, Magnetoencephalography, Speech

Progress in neurobiology (2021), Vol. 203 (34033856) (1 citation)

Shorter P1m Response in Children with Autism Spectrum Disorder without Intellectual Disabilities (2021)

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ABSTRACT (1) Background: Atypical auditory perception has been reported in individuals with autism spectrum disorder (ASD). Altered auditory evoked brain responses are also associated with childhood ASD. They are likely to be associated with atypical brain maturation. (2) Methods: This study examined children aged 5-8 years old: 29 with ASD but no intellectual disability and 46 age-matched typically developed (TD) control participants. Using magnetoencephalography (MEG) data obtained while participants listened passively to sinusoidal pure tones, bilateral auditory cortical response (P1m) was examined. (3) Results: Significantly shorter P1m latency in the left hemisphere was found for children with ASD without intellectual disabilities than for children with TD. Significant correlation between P1m latency and language conceptual ability was found in children with ASD, but not in children with TD. (4) Conclusions: These findings demonstrated atypical brain maturation in the auditory processing area in children with ASD without intellectual disability. Findings also suggest that ASD has a common neural basis for pure-tone sound processing and language development. Development of brain networks involved in language concepts in early childhood ASD might differ from that in children with TD.

Keywords: P1m response, auditory cortex, autism spectrum disorder, magnetoencephalography

International journal of molecular sciences (2021), Vol. 22, No. 5 (33807635) (0 citations)

Children with autism spectrum disorder show altered functional connectivity and abnormal maturation trajectories in response to inverted faces (2021)

Mamashli, Fahimeh; Kozhemiako, Nataliia; Khan, Sheraz; Nunes, Adonay S; McGuiggan, Nicole M; Losh, Ainsley; Joseph, Robert M; Ahveninen, Jyrki; Doesburg, Sam M; Hämäläinen, Matti S; Kenet, Tal

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ABSTRACT The processing of information conveyed by faces is a critical component of social communication. While the neurophysiology of processing upright faces has been studied extensively in autism spectrum disorder (ASD), less is known about the neurophysiological abnormalities associated with processing inverted faces in ASD. We used magnetoencephalography (MEG) to study both long-range and local functional connectivity, with the latter assessed using local cross-frequency coupling, in response to inverted faces stimuli, in 7-18 years old individuals with ASD and age and IQ matched typically developing (TD) individuals. We found abnormally reduced coupling between the phase of the alpha rhythm and the amplitude of the gamma rhythm in the fusiform face area (FFA) in response to inverted faces, as well as reduced long-range functional connectivity between the FFA and the inferior frontal gyrus (IFG) in response to inverted faces in the ASD group. These group differences were absent in response to upright faces. The magnitude of functional connectivity between the FFA and the IFG was significantly correlated with the severity of ASD, and FFA-IFG long-range functional connectivity increased with age in TD group, but not in the ASD group. Our findings suggest that both local and long-range functional connectivity are abnormally reduced in children with ASD when processing inverted faces, and that the pattern of abnormalities associated with the processing of inverted faces differs from the pattern of upright faces in ASD, likely due to the presumed greater reliance on top-down regulations necessary for efficient processing of inverted faces. LAY SUMMARY: We found alterations in the neurophysiological responses to inverted faces in children with ASD, that were not reflected in the evoked responses, and were not observed in the responses to upright faces. These alterations included reduced local functional connectivity in the fusiform face area (FFA), and decreased long-range alpha-band modulated functional connectivity between the FFA and the left IFG. The magnitude of long-range functional connectivity between the FFA and the inferior frontal gyrus was correlated with the severity of ASD.

Keywords: autism spectrum disorder, functional connectivity, inverted faces, phase-amplitude coupling

Autism research: official journal of the International Society for Autism Research (2021), Vol. 14, No. 6 (33709531) (0 citations)

Peak Alpha Frequency and Thalamic Structure in Children with Typical Development and Autism Spectrum Disorder (2022)

Green, Heather L; Dipiero, Marissa; Koppers, Simon; Berman, Jeffrey I; Bloy, Luke; Liu, Song; McBride, Emma; Ku, Matthew; Blaskey, Lisa; Kuschner, Emily; Airey, Megan; Kim, Mina; Konka, Kimberly; Roberts, Timothy P L; Edgar, J Christopher

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ABSTRACT Associations between age, resting-state (RS) peak-alpha-frequency (PAF = frequency showing largest amplitude alpha activity), and thalamic volume (thalamus thought to modulate alpha activity) were examined to understand differences in RS alpha activity between children with autism spectrum disorder (ASD) and typically-developing children (TDC) noted in prior studies. RS MEG and structural-MRI data were obtained from 51 ASD and 70 TDC 6- to 18-year-old males. PAF and thalamic volume maturation were observed in TDC but not ASD. Although PAF was associated with right thalamic volume in TDC (R[2] = 0.12, p = 0.01) but not ASD (R[2] = 0.01, p = 0.35), this group difference was not large enough to reach significance. Findings thus showed unusual maturation of brain function and structure in ASD as well as an across-group thalamic contribution to alpha rhythms.

Keywords: Alpha, Autism spectrum disorder, Magnetic resonance imaging, Magnetoencephalography, Maturation, Resting-state, Thalamic volume

Journal of autism and developmental disorders (2022), Vol. 52, No. 1 (33629214) (0 citations)

Atypical spatiotemporal activation of cerebellar lobules during emotional face processing in adolescents with autism (2021)

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ABSTRACT Autism spectrum disorder (ASD) is characterized by social deficits and atypical facial processing of emotional expressions. The underlying neuropathology of these abnormalities is still unclear. Recent studies implicate cerebellum in emotional processing; other

studies show cerebellar abnormalities in ASD. Here, we elucidate the spatiotemporal activation of cerebellar lobules in ASD during emotional processing of happy and angry faces in adolescents with ASD and typically developing (TD) controls. Using magnetoencephalography, we calculated dynamic statistical parametric maps across a period of 500 ms after emotional stimuli onset and determined differences between group activity to happy and angry emotions. Following happy face presentation, adolescents with ASD exhibited only left-hemispheric cerebellar activation in a cluster extending from lobule VI to lobule V (compared to TD controls). Following angry face presentation, adolescents with ASD exhibited only midline cerebellar activation (posterior IX vermis). Our findings indicate an early (125-175 ms) overactivation in cerebellar activity only for happy faces and a later overactivation for both happy (250-450 ms) and angry (250-350 ms) faces in adolescents with ASD. The prioritized hemispheric activity (happy faces) could reflect the promotion of a more flexible and adaptive social behavior, while the latter midline activity (angry faces) may guide conforming behavior.

Keywords: adolescence, autism spectrum disorder, cerebellum, emotions, face processing, magnetoencephalography

Human brain mapping (2021), Vol. 42, No. 7 (33528852) (0 citations)

Aberrant brain oscillatory coupling from the primary motor cortex in children with autism spectrum disorders (2021)

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ABSTRACT Autism spectrum disorder (ASD) often involves dysfunction in general motor control and motor coordination, in addition to core symptoms. However, the neural mechanisms underlying motor dysfunction in ASD are poorly understood. To elucidate this issue, we focused on brain oscillations and their coupling in the primary motor cortex (M1). We recorded magnetoencephalography in 18 children with ASD, aged 5 to 7 years, and 19 age- and IQ-matched typically-developing children while they pressed a button during a video-game-like motor task. The motor-related gamma (70 to 90 Hz) and pre-movement beta oscillations (15 to 25 Hz) were analyzed in the primary motor cortex using an inverse method. To determine the coupling between beta and gamma oscillations, we applied phase-amplitude coupling to calculate the statistical dependence between the amplitude of fast oscillations and the phase of slow oscillations. We observed a motor-related gamma increase and a pre-movement beta decrease in both groups. The ASD group exhibited a reduced motor-related gamma increase and enhanced pre-movement beta decrease in the ipsilateral primary motor cortex. We found phase-amplitude coupling, in which high-gamma activity was modulated by the beta rhythm in the primary motor cortex. Phase-amplitude

coupling in the ipsilateral primary motor cortex was reduced in the ASD group compared with the control group. Using oscillatory changes and their couplings, linear discriminant analysis classified the ASD and control groups with high accuracy (area under the receiver operating characteristic curve: 97.1%). The current findings revealed alterations in oscillations and oscillatory coupling, reflecting the dysregulation of motor gating mechanisms in ASD. These results may be helpful for elucidating the neural mechanisms underlying motor dysfunction in ASD, suggesting the possibility of developing a biomarker for ASD diagnosis.

Keywords: Autism spectrum disorder, Brain oscillations, Magnetoencephalography, Motor cortex, Phase-amplitude coupling

NeuroImage. Clinical (2021), Vol. 29 (33494029) (0 citations)

MEG-PLAN: a clinical and technical protocol for obtaining magnetoencephalography data in minimally verbal or nonverbal children who have autism spectrum disorder (2021)

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BACKGROUND Neuroimaging research on individuals who have autism spectrum disorder (ASD) has historically been limited primarily to those with age-appropriate cognitive and language performance. Children with limited abilities are frequently excluded from such neuroscience research given anticipated barriers like tolerating the loud sounds associated with magnetic resonance imaging and remaining still during data collection. To better understand brain function across the full range of ASD there is a need to (1) include individuals with limited cognitive and language performance in neuroimaging research (non-sedated, awake) and (2) improve data quality across the performance range. The purpose of this study was to develop, implement, and test the feasibility of a clinical/behavioral and technical protocol for obtaining magnetoencephalography (MEG) data. Participants were 38 children with ASD (8-12 years) meeting the study definition of minimally verbal/nonverbal language. MEG data were obtained during a passive pure-tone auditory task.

RESULTS Based on stakeholder feedback, the MEG Protocol for Low-language/cognitive Ability Neuroimaging (MEG-PLAN) was developed, integrating clinical/behavioral and technical components to be implemented by an interdisciplinary team (clinicians, behavior specialists, scientists, and technologists). Using MEG-PLAN, a 74% success rate was achieved for acquiring MEG data, with a 71% success rate for evaluable and analyzable data. Exploratory analyses suggested nonverbal IQ and adaptive skills were related to reaching the point of acquirable data. No differences in group characteristics were observed between those with acquirable versus evaluable/analyzable data. Examination of data quality (evaluable trial count) was acceptable. Moreover, results were reproducible, with high intraclass correlation coefficients for pure-tone auditory latency.

CONCLUSIONS Children who have ASD who are minimally verbal/nonverbal, and often have co-occurring cognitive impairments, can be effectively and comfortably supported to complete an electrophysiological exam that yields valid and reproducible results. MEG-PLAN is a protocol that can be disseminated and implemented across research teams and adapted across technologies and neurodevelopmental disorders to collect electrophysiology and neuroimaging data in previously understudied groups of individuals.

Keywords: Applied behavior analysis, Autism spectrum disorder, Compliance, Imaging methodology, Intellectual disability, Magnetoencephalography, Minimally verbal, Nonverbal

Journal of neurodevelopmental disorders (2021), Vol. 13, No. 1 (33485311) (0 citations)

Left hemispheric deficit in the sustained neuromagnetic response to periodic click trains in children with ASD (2020)

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BACKGROUND Deficits in perception and production of vocal pitch are often observed in people with autism spectrum disorder (ASD), but the neural basis of these deficits is unknown. In magnetoencephalogram (MEG), spectrally complex periodic sounds trigger two continuous neural responses-the auditory steady state response (ASSR) and the sustained field (SF). It has been shown that the SF in neurotypical individuals is associated with low-level analysis of pitch in the 'pitch processing center' of the Heschl's gyrus. Therefore, alternations in this auditory response may reflect atypical processing of vocal pitch. The SF, however, has never been studied in people with ASD.

METHODS We used MEG and individual brain models to investigate the ASSR and SF evoked by monaural 40 Hz click trains in boys with ASD (N = 35) and neurotypical (NT) boys (N = 35) aged 7-12-years.

RESULTS In agreement with the previous research in adults, the cortical sources of the SF in children were located in the left and right Heschl's gyri, anterolateral to those of the ASSR. In both groups, the SF and ASSR dominated in the right hemisphere and were higher in the hemisphere contralateral to the stimulated ear. The ASSR increased with age in both NT and ASD children and did not differ between the groups. The SF amplitude did not significantly change between the ages of 7 and 12 years. It was moderately attenuated in both hemispheres and was markedly delayed and displaced in the left hemisphere in boys with ASD. The SF delay in participants with ASD was present irrespective of their intelligence level and severity of autism symptoms.

LIMITATIONS We did not test the language abilities of our participants. Therefore, the link between SF and processing of vocal pitch in children with ASD remains speculative.

CONCLUSION Children with ASD demonstrate atypical processing of spectrally complex periodic sound at the level of the core auditory cortex of the left-hemisphere. The observed neural deficit may contribute to speech perception difficulties experienced by children with ASD, including their poor perception and production of linguistic prosody.

Keywords: 40 Hz clicks, Auditory steady state response (ASSR), Autism spectrum disorders (ASD), Children, Magnetoencephalogram (MEG), Pitch processing, Sustained field (SF)

Molecular autism (2020), Vol. 11, No. 1 (33384021) (9 citations)

Alpha connectivity and inhibitory control in adults with autism spectrum disorder (2020)

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BACKGROUND Individuals with autism spectrum disorder (ASD) often report difficulties with inhibition in everyday life. During inhibition tasks, adults with ASD show reduced activation of and connectivity between brain areas implicated in inhibition, suggesting impairments in inhibitory control at the neural level. Our study further investigated these differences by using magnetoencephalography (MEG) to examine

the frequency band(s) in which functional connectivity underlying response inhibition occurs, as brain functions are frequency specific, and whether connectivity in certain frequency bands differs between adults with and without ASD.

METHODS We analysed MEG data from 40 adults with ASD (27 males; 26.94 ± 6.08 years old) and 39 control adults (27 males; 27.29 ± 5.94 years old) who performed a Go/No-go task. The task involved two blocks with different proportions of No-go trials: Inhibition (25% No-go) and Vigilance (75% No-go). We compared whole-brain connectivity in the two groups during correct No-go trials in the Inhibition vs. Vigilance blocks between 0 and 400 ms.

RESULTS Despite comparable performance on the Go/No-go task, adults with ASD showed reduced connectivity compared to controls in the alpha band (8-14 Hz) in a network with a main hub in the right inferior frontal gyrus. Decreased connectivity in this network predicted more self-reported difficulties on a measure of inhibition in everyday life.

LIMITATIONS Measures of everyday inhibitory control were not available for all participants, so this relationship between reduced network connectivity and inhibitory control abilities may not be necessarily representative of all adults with ASD or the larger ASD population. Further research with independent samples of adults with ASD, including those with a wider range of cognitive abilities, would be valuable.

CONCLUSIONS Our findings demonstrate reduced functional brain connectivity during response inhibition in adults with ASD. As alpha-band synchrony has been linked to top-down control mechanisms, we propose that the lack of alpha synchrony observed in our ASD group may reflect difficulties in suppressing task-irrelevant information, interfering with inhibition in real-life situations.

Keywords: Alpha, Autism, Connectivity, Go/No-go, Inhibition, MEG

Molecular autism (2020), Vol. 11, No. 1 (33287904) (0 citations)

Predictive Processing during a Naturalistic Statistical Learning Task in ASD (2020)

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ABSTRACT Children's sensitivity to regularities within the linguistic stream, such as the likelihood that syllables co-occur, is foundational to speech segmentation and language acquisition. Yet, little is known about the neurocognitive mechanisms underlying speech segmentation in typical development and in neurodevelopmental disorders that impact language acquisition such as autism spectrum disorder (ASD). Here, we investigate the neural signals of statistical learning in 15 human participants (children ages 8-12) with a clinical diagnosis of ASD and 14 age-matched and gender-matched typically developing peers. We tracked the evoked neural responses to syllable sequences in a naturalistic statistical learning corpus using magnetoencephalography (MEG) in the left primary auditory cortex, posterior superior temporal gyrus (pSTG), and inferior frontal gyrus (IFG), across three repetitions of the passage. In typically developing children, we observed a neural index of learning in all three regions of interest (ROIs), measured by the change in evoked response amplitude as a function of syllable surprisal across passage repetitions. As surprisal increased, the amplitude of the neural response increased; this sensitivity emerged after repeated exposure to the corpus.

Children with ASD did not show this pattern of learning in all three regions. We discuss two possible hypotheses related to children's sensitivity to bottom-up sensory deficits and difficulty with top-down incremental processing.

Keywords: ASD, MEG, development, language, statistical learning

eNeuro (2020), Vol. 7, No. 6 (33199412) (0 citations)

Characterizing Inscapes and resting-state in MEG: Effects in typical and atypical development (2021)

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ABSTRACT Examining the brain at rest is a powerful approach used to understand the intrinsic properties of typical and disordered human brain function, yet task-free paradigms are associated with greater head motion, particularly in young and/or clinical populations such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Inscapes, a non-social and non-verbal movie paradigm, has been introduced to increase attention, thus mitigating head motion, while reducing the task-induced activations found during typical movie watching. Inscapes has not yet been validated for use in magnetoencephalography (MEG), and it has yet to be shown whether its effects are stable in clinical populations. Across typically developing (N = 32) children and adolescents and those with ASD (N = 46) and ADHD (N = 42), we demonstrate that head motion is reduced during Inscapes. Due to the task state evoked by movie paradigms, we also expectedly observed concomitant modulations in local neural activity (oscillatory power) and functional connectivity (phase and envelope coupling) in intrinsic resting-state networks and across the frequency spectra compared to a fixation cross resting-state. Increases in local activity were accompanied by decreases in low-frequency connectivity within and between resting-state networks, primarily the visual network, suggesting that task-state evoked by Inscapes moderates ongoing and spontaneous cortical inhibition that forms the idling intrinsic networks found during a fixation cross resting-state. Importantly, these effects were similar in ASD and ADHD, making Inscapes a well-suited advancement for investigations of resting brain function in young and clinical populations.

Keywords: Attention-deficit/hyperactivity disorder, Autism spectrum disorder, Inscapes, Magnetoencephalography, Neurodevelopmental disorders, Resting-state

NeuroImage (2021), Vol. 225 (33147510) (4 citations)

MEG Theta during Lexico-Semantic and Executive Processing Is Altered in High-Functioning Adolescents with Autism (2021)

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ABSTRACT Neuroimaging studies have revealed atypical activation during language and executive tasks in individuals with autism spectrum disorders (ASD). However, the spatiotemporal stages of processing associated with these dysfunctions remain poorly understood. Using an anatomically constrained magnetoencephalography approach, we examined event-related theta oscillations during a double-duty lexical decision task that combined demands on lexico-semantic processing and executive functions. Relative to typically developing peers, high-functioning adolescents with ASD had lower performance accuracy on trials engaging selective semantic retrieval and cognitive control. They showed an early overall theta increase in the left fusiform cortex followed by greater activity in the left-lateralized temporal (starting at ~250 ms) and frontal cortical areas (after ~450 ms) known to contribute to language processing. During response preparation and execution, the ASD group exhibited elevated theta in the anterior cingulate cortex, indicative of greater engagement of cognitive control. Simultaneously increased activity in the ipsilateral motor cortex may reflect a less lateralized and suboptimally organized motor circuitry. Spanning early sensory-specific and late response selection stages, the higher event-related theta responsivity in ASD may indicate compensatory recruitment to offset inefficient lexico-semantic retrieval under cognitively demanding conditions. Together, these findings provide further support for atypical language and executive functions in high-functioning ASD.

Keywords: MEG, Theta oscillations, autism, cognitive control, language

Cerebral cortex (New York, N.Y.: 1991) (2021), Vol. 31, No. 2 (33073290) (1 citation)

Autonomic and Electrophysiological Evidence for Reduced Auditory Habituation in Autism (2021)

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ABSTRACT It is estimated that nearly 90% of children on the autism spectrum exhibit sensory atypicalities. What aspects of sensory processing are affected in autism? Although sensory processing can be studied along multiple dimensions, two of the most basic ones involve examining instantaneous sensory responses and how the responses change over time. These correspond to the dimensions of 'sensitivity' and 'habituation'. Results thus far have indicated that autistic individuals do not differ systematically from controls in sensory acuity/sensitivity. However, data from studies of habituation have been equivocal. We have studied habituation in autism using two measures: galvanic skin response (GSR) and magneto-encephalography (MEG). We report data from two independent studies. The first study, was conducted with 13 autistic and 13 age-matched neurotypical young adults and used GSR to assess response to an extended metronomic sequence. The second study involved 24 participants (12 with an ASD diagnosis), different from those in study 1, spanning the pre-adolescent to young adult age range, and used MEG. Both studies reveal consistent patterns of reduced habituation in autistic participants. These results suggest that autism, through mechanisms that are yet to be elucidated, compromises a fundamental aspect of sensory processing, at least in the auditory domain. We discuss the implications for understanding sensory hypersensitivities, a hallmark phenotypic feature of autism, recently proposed theoretical accounts,

and potential relevance for early detection of risk for autism.

Keywords: Autism, GSR, Habituation, Hypersensitivities, MEG

Journal of autism and developmental disorders (2021), Vol. 51, No. 7 (32926307) (3 citations)

A Multimodal Study of the Contributions of Conduction Velocity to the Auditory Evoked Neuromagnetic Response: Anomalies in Autism Spectrum Disorder (2020)

Roberts, Timothy P L; Bloy, Luke; Ku, Matt; Blaskey, Lisa; Jackel, Carissa R; Edgar, James Christopher; Berman, Jeffrey I

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ABSTRACT This multimodal imaging study used magnetoencephalography, diffusion magnetic resonance imaging (MRI), and gamma-aminobutyric acid (GABA) magnetic resonance spectroscopy (MRS) to identify and contrast the multiple physiological mechanisms associated with auditory processing efficiency in typically developing (TD) children and children with autism spectrum disorder (ASD). Efficient transmission of auditory input between the ear and auditory cortex is necessary for rapid encoding of auditory sensory information. It was hypothesized that the M50 auditory evoked response latency would be modulated by white matter microstructure (indexed by diffusion MRI) and by tonic inhibition (indexed by GABA MRS). Participants were 77 children diagnosed with ASD and 40 TD controls aged 7-17 years. A model of M50 latency with auditory radiation fractional anisotropy and age as independent variables was able to predict 52% of M50 latency variance in TD children, but only 12% of variance in ASD. The ASD group exhibited altered patterns of M50 latency modulation characterized by both higher variance and deviation from the expected structure-function relationship established with the TD group. The TD M50 latency model was used to identify a subpopulation of ASD who are significant "outliers" to the TD model. The ASD outlier group exhibited unexpectedly long M50 latencies in conjunction with significantly lower GABA levels. These findings indicate the dependence of electrophysiologic sensory response latency on underlying microstructure (white matter) and neurochemistry (synaptic activity). This study demonstrates the use of biologically based measures to stratify ASD according to their brain-level "building blocks" as an alternative to their behavioral phenotype. LAY SUMMARY: Children with ASD often have a slower brain response when hearing sounds. This study used multiple brain imaging techniques to examine the structural and neurochemical factors which control the brain's response time to auditory tones in children with ASD and TD children. The relationship between brain imaging measures and brain response time was also used to identify ASD subgroups. Autism Res 2020, 13: 1730-1745. © 2020 International Society for Autism Research and Wiley Periodicals LLC.

Keywords: MR spectroscopy, autism spectrum disorder, conduction velocity, diffusion MRI, magnetoencephalography, multimodal imaging

Autism research: official journal of the International Society for Autism Research (2020), Vol. 13, No. 10 (32924333) (8 citations)

Markers for the central serotonin system correlate to verbal ability and paralinguistic social voice processing in autism spectrum disorder (2020)

Yoshimura, Yuko; Kikuchi, Mitsuru; Saito, Daisuke N; Hirosawa, Tetsu; Takahashi, Tetsuya; Munesue, Toshio; Kosaka, Hirotaka; Naito, Nobushige; Ouchi, Yasuomi; Minabe, Yoshio

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ABSTRACT Impairment in verbal communication abilities has been reported in autism spectrum disorder (ASD). Dysfunction of the serotonergic system has also been reported in ASD. However, it is still unknown how the brain serotonergic system relates to impairment in verbal communication abilities in individuals with ASD. In the present study, we investigated the correlation between brain serotonergic condition and brain sensitivity to paralinguistic stimuli (i.e., amplitude in the human voice prosodic change-evoked mismatch field) measured by magnetoencephalography (MEG) or verbal ability in 10 adults with ASD. To estimate the brain serotonergic condition, we measured the serotonin transporter nondisplaceable binding potential cerebrum-wide using positron emission tomography with [11C]N,N-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([11C] DASB). The results demonstrated a significant positive correlation between brain activity to paralinguistic stimuli and brain serotonin transporter binding potential in the left lingual gyrus, left fusiform gyrus and left calcarine cortex. In addition, there were significant positive correlations between verbal ability and serotonergic condition in the right anterior insula, right putamen and right central operculum. These results suggested that the occipital cortex is implicated in recognition of the prosodic change in ASD, whereas the right insula-involved serotonergic system is important in nurturing verbal function in ASD.Trial registration: UMIN000011077.

Scientific reports (2020), Vol. 10, No. 1 (32883965) (1 citation)

Altered Connectivity During a False-Belief Task in Adults With Autism Spectrum Disorder (2020)

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BACKGROUND Deficits in social communication are one of the main features of autism spectrum disorder (ASD). Adults with ASD show atypical brain activity during false-belief understanding, an aspect of social communication involving the ability to infer that an individual can have an incorrect belief about a situation. Our study is the first to investigate whether adults with ASD exhibit differences in frequency-specific functional connectivity patterns during false-belief reasoning.

METHODS We used magnetoencephalography to contrast functional connectivity underlying false-belief understanding between 40 adults with ASD and 39 control adults. We examined whole-brain phase synchrony measures during a false-belief task in 3 frequency bands: theta (4-7 Hz), alpha (8-14 Hz), and beta (15-30 Hz).

RESULTS Adults with ASD demonstrated reduced theta-band connectivity compared with control adults between several right-lateralized and midline regions such as the medial prefrontal cortex, right temporo-parietal junction, right inferior frontal gyrus, and right superior temporal gyrus. During false-belief trials, they

also recruited a network in the beta band that included primary visual regions such as the bilateral inferior occipital gyri and the left anterior temporoparietal junction.

CONCLUSIONS Reduced theta-band synchrony between areas associated with mentalizing, inhibition, and visual processing implies some difficulty in communication among these functions in ASD. This impairment in top-down control in the theta band may be counterbalanced by their engagement of a beta-band network because both the left anterior temporoparietal junction and beta-band oscillations are associated with attentional processes. Thus, adults with ASD demonstrate alternative neural mechanisms for successful false-belief reasoning.

Keywords: Autism, Beta, Connectivity, False belief, MEG, Theta

Biological psychiatry. Cognitive neuroscience and neuroimaging (2020), Vol. 5, No. 9 (32600899) (6 citations)

Relationship between epileptiform discharges and social reciprocity or cognitive function in children with and without autism spectrum disorders: An MEG study (2020)

Hirosawa, Tetsu; Sowman, Paul F; Fukai, Mina; Kameya, Masafumi; Soma, Daiki; Hino, Shoryoku; Kitamura, Tatsuru; An, Kyung-Min; Yoshimura, Yuko; Hasegawa, Chiaki; Saito, Daisuke; Ikeda, Takashi; Kikuchi, Mitsuru

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Psychiatry and clinical neurosciences (2020), Vol. 74, No. 9 (32588484) (1 citation)

Magnetoencephalography Research in Pediatric Autism Spectrum Disorder (2020)

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ABSTRACT Magnetoencephalography (MEG) research indicates differences in neural brain measures in children with autism spectrum disorder (ASD) compared to typically developing (TD) children. As reviewed here, resting-state MEG exams are of interest as well as MEG paradigms that assess neural function across domains (e.g., auditory, resting state). To date, MEG research has primarily focused on group-level differences. Research is needed to explore whether MEG measures can predict, at the individual level, ASD diagnosis, prognosis (future severity), and response to therapy.

Keywords: ASD, Biomarker, ERD, M100, M50, MEG, MMF

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336406) (2 citations)

Significance of Beta-Band Oscillations in Autism Spectrum Disorders During Motor Response Inhibition Tasks: A MEG Study (2020)

Moliadze, Vera; Brodski-Guerniero, Alla; Schuetz, Magdalena; Siemann, Julia; Lyzhko, Ekaterina; Schlitt, Sabine; Kitzerow, Janina; Langer, Anne; Kaiser, Jochen; Naumer, Marcus J; Wibral, Michael; Chan, Jason; Freitag, Christine M; Siniatchkin, Michael

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ABSTRACT In Autism Spectrum Disorders (ASD), impaired response inhibition and lack of adaptation are hypothesized to underlie core ASD symptoms, such as social communication and repetitive, stereotyped behavior. Thus, the aim of the present study was to compare neural correlates of inhibition, post-error adaptation, and reaction time variability in ASD and neuro-typical control (NTC) participants by investigating possible differences in error-related changes of oscillatory MEG activity. Twelve male NTC (mean age 20.3 ± 3.7) and fourteen male patients with ASD (mean age 17.8 ± 2.9) were included in the analysis. Subjects with ASD showed increased error-related reaction time variability. MEG analysis revealed decreased beta power in the ASD group in comparison to the NTC group over the centro-parietal channels in both, the pre-stimulus and post-response interval. In the ASD group, mean centro-parietal beta power negatively correlated with dimensional autism symptoms. In both groups, false alarms were followed by an early increase in temporo-frontal theta to alpha power; and by a later decrease in alpha to beta power at central and posterior sensors. Single trial correlations were additionally studied in the ASD group, who showed a positive correlation of pre-stimulus beta power with post-response theta, alpha, and beta power, particularly after hit trials. On a broader scale, the results deliver important insights into top-down control deficits that may relate to core symptoms observed in ASD.

Keywords: ASD, Beta-band oscillations, MEG, Motor response inhibition

Brain topography (2020), Vol. 33, No. 3 (32303950) (2 citations)

Auditory steady-state response at 20 Hz and 40 Hz in young typically developing children and children with autism spectrum disorder (2020)

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AIM The early detection of autistic tendencies in children is essential for providing proper care and education. The auditory steady-state response (ASSR) provides a passive, non-invasive technique for assessing neural synchrony at specific response frequencies in many mental disorders, including autism spectrum disorder (ASD), but few studies have investigated its use in young children. This study investigated the ASSR at 20 Hz and 40 Hz in typically developing (TD) children and children with ASD aged 5-7 years.

METHODS The participants were 23 children with ASD and 32 TD children aged 5-7 years. Using a custom-made magnetoencephalography device, we measured ASSR at 20 Hz and 40 Hz, compared the results between groups, and evaluated the association with intellectual function as measured by Kaufmann Assessment Battery for Children.

RESULTS Responses to 20 Hz and 40 Hz were clearly detected in both groups with no significant difference identified. Consistent with previous findings, right dominance of the 40-Hz ASSR was observed in both groups. In the TD children, the right-side 40-Hz ASSR

was correlated with age. The Kaufmann Assessment Battery for Children score was correlated with the left-side 40-Hz ASSR in both groups.

CONCLUSION Right-dominant ASSR was successfully detected in young TD children and children with ASD. No difference in ASSR was observed between the children with ASD and the TD children, although the right-side 40-Hz ASSR increased with age only in the TD children. Left-side 40-Hz ASSR was associated with intelligence score in both groups.

Keywords: auditory steady-state response, autism spectrum disorder, development, magnetoencephalography

Psychiatry and clinical neurosciences (2020), Vol. 74, No. 6 (32155301) (10 citations)

Evaluating motor cortical oscillations and age-related change in autism spectrum disorder (2020)

Gaetz, William; Rhodes, Edward; Bloy, Luke; Blaskey, Lisa; Jackel, Carissa R; Brodkin, Edward S; Waldman, Amy; Embick, David; Hall, Stephen; Roberts, Timothy P L

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ABSTRACT Autism spectrum disorder (ASD) is primarily characterized by impairments in social communication and the appearance of repetitive behaviors with restricted interests. Increasingly, evidence also points to a general deficit of motor tone and coordination in children and adults with ASD; yet the neural basis of motor functional impairment in ASD remains poorly characterized. In this study, we used magnetoencephalography (MEG) to (1) assess potential group differences between typically developing (TD) and ASD participants in motor cortical oscillatory activity observed on a simple button-press task and (2) to do so over a sufficiently broad age-range so as to capture age-dependent changes associated with development. Event-related desynchronization was evaluated in Mu (8-13 Hz) and Beta (15-30 Hz) frequency bands (Mu-ERD, Beta-ERD). In addition, post-movement Beta rebound (PMBR), and movement-related gamma (60-90 Hz) synchrony (MRGS) were also assessed in a cohort of 123 participants (63 typically developing (TD) and 59 with ASD) ranging in age from 8 to 24.9 years. We observed significant age-dependent linear trends in Beta-ERD and MRGS power with age for both TD and ASD groups; which did not differ significantly between groups. However, for PMBR, in addition to a significant effect of age, we also observed a significant reduction in PMBR power in the ASD group ($p < 0.05$). Post-hoc tests showed that this omnibus group difference was driven by the older cohort of children >13.2 years ($p < 0.001$) and this group difference was not observed when assessing PMBR activity for the younger PMBR groups (ages 8-13.2 years; $p = 0.48$). Moreover, for the older ASD cohort, hierarchical regression showed a significant relationship between PMBR activity and clinical scores of ASD severity (Social Responsiveness Scale (SRS T scores)), after regressing out the effect of age ($p < 0.05$). Our results show substantial age-dependent changes in motor cortical oscillations (Beta-ERD and MRGS) occur for both TD and ASD children and diverge only for PMBR, and most significantly for older adolescents and adults with ASD. While the functional significance of PMBR and reduced PMBR signaling remains to be fully elucidated, these results underscore the importance of considering age as a factor when assessing motor cortical oscillations and group differences in children with ASD.

NeuroImage (2020), Vol. 207 (31726253) (10 citations)

Cortical excitation-inhibition ratio mediates the effect of pre-attentive auditory processing deficits on interpersonal difficulties (2020)

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ABSTRACT Several lines of evidence identify aberrant excitatory-inhibitory neural processes across autism and schizophrenia spectrum disorders, particularly within the psychosocial domain. Such neural processes include increased excitatory glutamate and reduced inhibitory GABA concentrations, which may affect auditory pre-attentive processing as indexed by the mismatch negativity (MMN); thus, an excitation-inhibition imbalance might lead to aberrant MMN, which might in turn drive the relationship between the MMN and psychosocial difficulties. This research has the potential to enhance the neurochemical understanding of the relationship between electrophysiology (MMN) and behavioural/clinical measures (psychosocial difficulties). Thirty-eight adults (18 male, 18-40 years) completed the Schizotypal Personality Questionnaire (SPQ) and Autism-Spectrum Quotient (AQ). Glutamate and GABA concentrations in bilateral superior temporal cortex (STC) were quantified using proton magnetic resonance spectroscopy (1H-MRS) while auditory MMN to a duration deviant was measured with magnetoencephalography. Spearman correlations probed the relationships between STC glutamate/GABA ratios, MMN amplitude and latency, and AQ and SPQ dimensions. Mediation effects of glutamate/GABA ratios on the relationship between MMN and AQ-SPQ dimensions were probed using causal mediation analysis. Only SPQ-interpersonal and AQ-communication were significantly correlated with right hemisphere glutamate/GABA ratios and MMN latency ($ps < 0.05$), which were themselves correlated ($p = .035$). Two mediation models were investigated, with right MMN latency as predictor and SPQ-interpersonal and AQ-communication as outcome variables. Right STC glutamate/GABA ratios significantly mediated the relationship between MMN latency and SPQ-interpersonal scores, but only partially mediated the relationship between MMN latency and AQ-communication scores. These findings support the growing body of literature pointing toward an excitation-inhibition imbalance that is central to psychosocial functioning across multi-dimensional spectrum disorders, such as autism and schizophrenia, and provides neurochemical indicators of the processes that underlie psychosocial dysfunction.

Keywords: Autism, GABA, Glutamate, Mismatch negativity, Schizophrenia, Social cognition

Progress in neuro-psychopharmacology & biological psychiatry (2020), Vol. 98 (31676468) (2 citations)

Emotional face processing in autism spectrum disorder: Effects in gamma connectivity (2020)

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ABSTRACT Impairments in social functioning are characteristic of autism spectrum disorder (ASD). Differences in functional networks during face processing in ASD compared to controls have been reported; however,

the spatial-temporal dynamics of networks underlying affective processing are still not well understood. The current magnetoencephalography study examined whole-brain functional connectivity to implicit happy and angry faces in 104 adults with and without ASD. A network of reduced gamma band (30-55 Hz) phase synchrony occurring 80-308 ms following angry face presentation was found in adults with ASD compared to controls. The network involved widespread connections primarily anchored in frontal regions, including bilateral orbitofrontal areas, bilateral inferior frontal gyri, and left middle frontal gyrus extending to occipital, temporal, parietal, and subcortical regions. This finding suggests disrupted long-range neuronal communication to angry faces. Additionally, reduced gamma band-specific connectivity may reflect altered E/I balance in brain regions critical for emotional face processing in ASD.

Keywords: ASD, Adulthood, Emotional face processing, Functional connectivity, Gamma band, Magnetoencephalography

Biological psychology (2020), Vol. 149 (31574296) (8 citations)

Bipolar Disorder

Gamma band VMPFC-PreCG.L connection variation after the onset of negative emotional stimuli can predict mania in depressive patients (2023)

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OBJECTIVE Because of the similar clinical symptoms, it is difficult to distinguish unipolar disorder (UD) from bipolar disorder (BD) in the depressive episode using the available clinical features, especially for those who meet the diagnostic criteria of UD, however, experience the manic episode during the follow-up (tBD).

METHODS Magnetoencephalography recordings during a sad expression recognition task were obtained from 81 patients (27 BD, 24 tBD, 30 UD) and 26 healthy controls (HCs). Source analysis was applied to localize 64 regions of interest in the low gamma band (30-50 Hz). Regional functional connections (FCs) were constructed respectively within three time periods (early: 0-200 ms, middle: 200-400 ms, and post: 400-600 ms). The network-based statistic method was used to explore the abnormal connection patterns in tBD compared to UD and HC. BD was applied to explore whether such abnormality is still significant between every two groups of BD, tBD, UD, and HC.

RESULTS The VMPFC-PreCG.L connection was found to be a significantly different connection between tBD and UD in the early time period and between tBD and BD in the middle time period. Furthermore, the middle/early time period ratio of FC value of VMPFC-PreCG.L connection was negatively correlated with the bipolarity index in tBD.

CONCLUSIONS The VMPFC-PreCG.L connection in different time periods after the onset of sad facial stimuli may be a potential biomarker to distinguish the different states of BD. The FC ratio of VMPFC-PreCG.L connection may predict whether patients with depressive episodes subsequently develop mania.

Keywords: Bipolar disorder, Magnetoencephalography, Network-based statistic, Unipolar disorder

Journal of psychiatric research (2023), Vol. 158 (36586215) (0 citations)

Convergent and divergent cognitive impairment of unipolar and bipolar depression: A magnetoencephalography resting-state study (2023)

Wang, HaoFei; Tian, Shui; Yan, Rui; Tang, Hao; Shi, JiaBo; Zhu, RongXin; Chen, Yu; Han, YingLin; Chen, ZhiLu; Zhou, HongLiang; Zhao, Shuai; Yao, ZhiJian; Lu, Qing

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BACKGROUND Unipolar depression (UD) and bipolar depression (BD) showed convergent and divergent cognitive impairments. Neural oscillations are linked to the foundational cognitive processes. We aimed to investigate the underpinning spectral neuronal power patterns by magnetoencephalography (MEG), which combinates high spatial and temporal resolution. We hypothesized that patients with UD and BD exhibit common and distinct patterns, which may contribute to their cognitive impairments.

METHODS Group cognitive tests were performed. Eyes closed resting-state MEG data were collected from 61 UD, 55 BD, and 52 healthy controls (HC). Nonparametric cluster-based permutation tests were performed to deal with the multiple comparison problem on channel-frequency MEG data. Correlation analysis of cognitive dysfunction scores and MEG oscillation were conducted by Spearman or partial correlation analysis.

RESULTS Wisconsin Card Sorting Test showed similar cognitive impairment in patients with UD and BD. Moreover, patients with BD exhibited extensive cognitive deficits in verbal executive functions and visuospatial processing. Compare to HC, both patients with UD and BD showed increased frontal-central beta power while high gamma power was decreased in UD groups during the resting-state. The significant correlations between cognitive function and average beta power were observed.

CONCLUSIONS Patients with BD had more cognitive impairments on different dimensions than those with UD, involving disrupted beta power modulations. Our investigation provides a better understanding of the neuroelectrophysiological process underlying cognitive impairments in patients with UD and BD.

Keywords: Bipolar depression, Cognitive impairment, MEG, Magnetoencephalography, Resting-state, Unipolar depression

Journal of affective disorders (2023), Vol. 321 (36181913) (0 citations)

MEG-based Classification and Grad-CAM Visualization for Major Depressive and Bipolar Disorders with Semi-CNN (2022)

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ABSTRACT Major depressive disorder (MDD) and bipolar disorder (BD) are two major mood disorders with partly overlapped symptoms but different treatments. However, their misdiagnosis and mistreatment are common based on the DSM-V criteria, lacking objective and quantitative indicators. This study aimed to develop a novel approach that accurately classifies MDD and BD based on their resting-state magnetoencephalography (MEG) signals during euthymic phases. A revisited 3D CNN model, Semi-CNN, that could automatically detect brainwave patterns in spatial, temporal, and frequency domains was implemented to classify wavelet-transformed MEG signals of normal controls and MDD and BD patients. The model achieved a test accuracy of 96.05% and an average of 95.71% accuracy for 5-fold cross-validation. Furthermore, saliency maps of the model were estimated using Grad-CAM++ to visualize the proposed classification model and highlight disease-specific brain regions and frequencies. Clinical Relevance - Our model provides a stable pipeline that accurately classifies MDD, BD, and healthy individuals based on resting-state MEG signals during the euthymic phases, opening the potential for quantitative and

accurate brain-based diagnosis for the highly misdiagnosed MDD/BD patients.

Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference (2022), Vol. 2022 (36086021) (0 citations)

The 40-Hz auditory steady-state response in bipolar disorder: A meta-analysis (2022)

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OBJECTIVE Bipolar disorder is characterized by aberrant neurophysiological responses as measured with electroencephalography (EEG) and magnetoencephalography (MEG), including the 40-Hz auditory steady-state response (ASSR). 40-Hz ASSR deficits are also found in patients with schizophrenia and may represent a transdiagnostic biomarker of neuronal circuit dysfunction. In this systematic review and meta-analysis, we summarize and evaluate the evidence for 40-Hz ASSR deficits in patients with bipolar disorder.

METHODS We identified studies from PubMed, EMBASE, and SCOPUS. We assessed the risk of bias, calculated Hedges' g meta-level effect sizes, and investigated small-study effects using funnel plots and Egger regression.

RESULTS Seven studies, comprising 396 patients with bipolar disorder and 404 healthy controls, were included in the meta-analysis. Studies displayed methodological heterogeneity and an overall high risk of bias. Patients with bipolar disorder showed consistent reductions in 40-Hz ASSR evoked power (Hedges' g = -0.49; 95% confidence intervals [-0.67, -0.31]) and inter-trial phase coherence (ITPC) (Hedges' g = -0.43; 95 %CI [-0.58, -0.29]) compared with healthy controls.

CONCLUSIONS Our meta-analysis provides evidence that 40-Hz ASSRs are reduced in patients with bipolar disorder compared with healthy controls.

SIGNIFICANCE Future large-scale studies are warranted to link 40-Hz ASSR deficits to clinical features and developmental trajectories.

Keywords: Bipolar disorder, Electroencephalography, Gamma rhythm, Magnetoencephalography, Meta-analysis, Systematic review

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2022), Vol. 141 (35853310) (2 citations)

Differences in verbal and spatial working memory in patients with bipolar II and unipolar depression: an MSI study (2021)

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BACKGROUND Depressive symptoms could be similarly expressed in bipolar and unipolar disorder. However, changes in cognition and brain networks might be quite distinct. We aimed to find out the difference in the neural mechanism of impaired working memory in patients with bipolar and unipolar disorder.

METHOD According to diagnostic criteria of bipolar II disorder of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and assessments, 13 bipolar II depression (BP II), 8 unipolar depression (UD) patients and 15 healthy controls (HC) were recruited in the study. We used 2-back tasks and magnetic source imaging (MSI) to test working memory functions and get the brain reactions of the participants.

RESULTS Compared with HC, only spatial working memory tasks accuracy was significantly worse in both UD and BP II ($p = 0.001$). Pearson correlation showed that the stronger the FCs' strength of MFG-IPL and IPL-preSMA, the higher accuracy of SWM task within left FPN in patients with UD ($r = 0.860$, $p = 0.006$; $r = 0.752$, $p = 0.031$). However, the FC strength of IFG-IPL was negatively correlated with the accuracy of SWM task within left FPN in patients with BP II ($r = -0.591$, $p = 0.033$).

CONCLUSIONS Our study showed that the spatial working memory of patients with whether UD or BP II was impaired. The patterns of FCs within these two groups of patients were different when performing working memory tasks.

Keywords: Depression, Frontoparietal network, Magnetoencephalography, Working memory

BMC psychiatry (2021), Vol. 21, No. 1 (34781922) (2 citations)

Magnetoencephalography resting-state spectral fingerprints distinguish bipolar depression and unipolar depression (2020)

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OBJECTIVES In clinical practice, bipolar depression (BD) and unipolar depression (UD) appear to have similar symptoms, causing BD being frequently misdiagnosed as UD, leading to improper treatment decision and outcome. Therefore, it is in urgent need of distinguishing BD from UD based on clinical objective biomarkers as early as possible. Here, we aimed to integrate brain neuroimaging data and an advanced machine learning technique to predict different types of mood disorder patients at the individual level.

METHODS Eyes closed resting-state magnetoencephalography (MEG) data were collected from 23 BD, 30 UD, and 31 healthy controls (HC). Individual power spectra were estimated by Fourier transform, and statistic spectral differences were assessed via a cluster permutation test. A support vector machine classifier was further applied to predict different mood disorder types based on discriminative oscillatory power.

RESULTS Both BD and UD showed decreased frontal-central gamma/beta ratios comparing to HC, in which gamma power (30-75 Hz) was decreased in BD while beta power (14-30 Hz) was increased in UD vs HC. The support vector machine model obtained significant high classification accuracies distinguishing three groups based on mean gamma and beta power (BD: 79.9%, UD: 81.1%, HC: 76.3%, $P < .01$).

CONCLUSIONS In combination with resting-state MEG data and machine learning technique, it is possible to make an individual and objective prediction for mode disorder types, which in turn has implications for diagnosis precision and treatment decision of mood disorder patients.

Keywords: MEG, bipolar depression, resting state, support vector machine, unipolar depression

Bipolar disorders (2020), Vol. 22, No. 6 (31729112) (9 citations)

Neurophysiology-Guided Laser Interstitial Thermal Therapy: A Synergistic Approach For Motor Function Preservation. Technical Note (2022)

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BACKGROUND Laser interstitial thermal therapy (LITT) is a minimally invasive ablative technique with specific indications for neuro-oncology, especially in the case of lesions in eloquent areas. Even being performed through a small catheter under stereotactic conditions, the risk of damaging vital structures such as white matter tracts or cortical eloquent areas is not negligible. The mechanism of damage can be related to catheter insertion or to excessive laser ablation. An accurate preoperative workup, aimed at locating the eloquent structures, can be combined with a real-time intraoperative neurophysiologic monitoring to reduce surgical morbidity while maximizing the efficacy of LITT.

METHODS We developed a synergistic approach for neurophysiology-guided LITT based on state-of-the-art technologies, namely, magnetoencephalography, diffusion tensor imaging, and intraoperative neurophysiologic monitoring.

RESULTS As a result, we improved the planning phase thanks to a more precise representation of functional structures that allows the simulation of different trajectories and the identification of the most suitable trajectory to treat the lesion while respecting the functional boundaries. Catheter insertion is conducted under continuous neurophysiologic feedback and the ablation phase is modeled on the functional boundaries identified by stimulation, allowing it to be extremely accurate.

CONCLUSIONS An integrated approached guided by neurophysiology is able to reduce the surgical morbidity even in a relatively accurate technique such as LITT. To the best of our knowledge, this represents the first report on this synergistic approach which could really impact the treatment of tumors in eloquent areas. Future studies are needed in the effort to implement this approach in functional or epilepsy neurosurgery as well.

Keywords: Imaging, LITT, MEG, Neuro-oncology, Neurophysiology, Rehearsal

World neurosurgery (2022), Vol. 168 (36202344) (1 citation)

Regional healthy brain activity, glioma occurrence and symptomatology (2022)

Numan, Tianne; Breedt, Lucas C; Maciel, Bernardo de A P C; Kulik, Shanna D; Derks, Jolanda; Schoonheim, Menno M; Klein, Martin; de Witt Hamer, Philip C; Miller, Julie J; Gerstner, Elizabeth R; Stufflebeam, Steven M; Hillebrand, Arjan; Stam, Cornelis J; Geurts, Jeroen J G; Reijneveld, Jaap C; Douw, Linda

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ABSTRACT It is unclear why exactly gliomas show preferential occurrence in certain brain areas. Increased spiking activity around gliomas leads to faster tumour growth in animal models, while higher non-invasively measured brain activity is related to shorter survival in patients. However, it is unknown how regional intrinsic brain activity, as measured in healthy controls, relates to glioma occurrence. We first investigated whether gliomas occur more frequently in regions with intrinsically higher brain activity. Second, we explored whether intrinsic cortical activity at individual patients' tumour locations relates to tumour and patient characteristics. Across three cross-sectional cohorts, 413 patients were included. Individual tumour masks were created. Intrinsic regional brain activity was assessed through resting-state magnetoencephalography acquired in healthy controls and source-localized to 210 cortical brain regions. Brain activity was operationalized as: (i) broadband power; and (ii) offset of the aperiodic component of the power spectrum, which both reflect neuronal spiking of the underlying neuronal population. We additionally assessed (iii) the slope of the aperiodic component of the power spectrum, which is thought to reflect the neuronal excitation/inhibition ratio. First, correlation coefficients were calculated between group-level regional glioma occurrence, as obtained by concatenating tumour masks across patients, and group-averaged regional intrinsic brain activity. Second, intrinsic brain activity at specific tumour locations was calculated by overlaying patients' individual tumour masks with regional intrinsic brain activity of the controls and was associated with tumour and patient characteristics. As proposed, glioma preferentially occurred in brain regions characterized by higher intrinsic brain activity in controls as reflected by higher offset. Second, intrinsic brain activity at patients' individual tumour locations differed according to glioma subtype and performance status: the most malignant isocitrate dehydrogenase-wild-type glioblastoma patients had the lowest excitation/inhibition ratio at their individual tumour locations as compared to isocitrate dehydrogenase-mutant, 1p/19q-codeleted glioma patients, while a lower excitation/inhibition ratio related to poorer Karnofsky Performance Status, particularly in codeleted glioma patients. In conclusion, gliomas more frequently occur in cortical brain regions with intrinsically higher activity levels, suggesting that more active regions are more vulnerable to glioma development. Moreover, indices of healthy, intrinsic excitation/inhibition ratio at patients' individual tumour locations may capture both tumour biology and patients' performance status. These findings contribute to our understanding of the complex and bidirectional relationship between normal brain functioning and glioma growth, which is at the core of the relatively new field of 'cancer neuroscience'.

Keywords: cancer neuroscience, magnetoencephalography, network neuroscience, neuro-oncology, primary brain tumours

Brain: a journal of neurology (2022), Vol. 145, No. 10 (36130310) (1 citation)

Non-invasively measured brain activity and radiological progression in diffuse glioma (2021)

Numan, T; Kulik, S D; Moraal, B; Reijneveld, J C; Stam, C J; de Witt Hamer, P C; Derks, J; Bruynzeel, A M E; van

Linde, M E; Wesseling, P; Kouwenhoven, M C M; Klein, M; Würdinger, T; Barkhof, F; Geurts, J J G; Hillebrand, A; Douw, L

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ABSTRACT Non-invasively measured brain activity is related to progression-free survival in glioma patients, suggesting its potential as a marker of glioma progression. We therefore assessed the relationship between brain activity and increasing tumor volumes on routine clinical magnetic resonance imaging (MRI) in glioma patients. Postoperative magnetoencephalography (MEG) was recorded in 45 diffuse glioma patients. Brain activity was estimated using three measures (absolute broadband power, offset and slope) calculated at three spatial levels: global average, averaged across the peritumoral areas, and averaged across the homologues of these peritumoral areas in the contralateral hemisphere. Tumors were segmented on MRI. Changes in tumor volume between the two scans surrounding the MEG were calculated and correlated with brain activity. Brain activity was compared between patient groups classified into having increasing or stable tumor volume. Results show that brain activity was significantly increased in the tumor hemisphere in general, and in peritumoral regions specifically. However, none of the measures and spatial levels of brain activity correlated with changes in tumor volume, nor did they differ between patients with increasing versus stable tumor volumes. Longitudinal studies in more homogeneous subgroups of glioma patients are necessary to further explore the clinical potential of non-invasively measured brain activity.

Scientific reports (2021), Vol. 11, No. 1 (34556701) (2 citations)

Understanding Global Brain Network Alterations in Glioma Patients (2021)

Derks, Jolanda; Kulik, Shanna D; Numan, Tianne; de Witt Hamer, Philip C; Noske, David P; Klein, Martin; Geurts, Jeroen J G; Reijneveld, Jaap C; Stam, Cornelis J; Schoonheim, Menno M; Hillebrand, Arjan; Douw, Linda

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ABSTRACT Introduction: Glioma patients show increased global brain network clustering related to poorer cognition and epilepsy. However, it is unclear whether this increase is spatially widespread, localized in the (peri)tumor region only, or decreases with distance from the tumor. Materials and Methods: Weighted global and local brain network clustering was determined in 71 glioma patients and 53 controls by using magnetoencephalography. Tumor clustering was determined by averaging local clustering of regions overlapping with the tumor, and vice versa for non-tumor regions. Euclidean distance was determined from the tumor centroid to the centroids of other regions. Results: Patients showed higher global clustering compared with controls. Clustering of tumor and non-tumor regions did not differ, and local clustering was not associated with distance from the tumor. Post hoc analyses revealed that in the patient group, tumors were located more often in regions with higher clustering in controls, but it seemed that tumors of patients with high global clustering were located more often in regions with lower clustering in controls. Conclusions: Glioma patients show non-local network disturbances. Tumors of patients with high global clustering may have a preferred localization, namely regions with lower clustering in controls, suggesting that tumor localization relates to the extent of network disruption. Impact statement This work uses the innovative framework of network neuroscience to investigate functional connectivity patterns associated with brain tumors. Glioma (primary brain tumor) patients experience cognitive deficits and epileptic seizures, which have been related to brain network alterations. This study shows that glioma patients have a spatially widespread increase in global network clustering, which cannot be attributed to local effects of the tumor. Moreover, tumors occur more often in brain regions with higher network clustering in controls. This study emphasizes the global character of network alterations in glioma patients and suggests that preferred tumor locations are characterized by particular network profiles.

Keywords: functional connectivity, glioma, magnetoencephalography, neuro-oncology, resting-state

Brain connectivity (2021), Vol. 11, No. 10 (33947274) (4 citations)

Oscillatory and structural signatures of language plasticity in brain tumor patients: A longitudinal study (2021)

Amoruso, Lucia; Geng, Shuang; Molinaro, Nicola; Timofeeva, Polina; Gisbert-Muñoz, Sandra; Gil-Robles, Santiago; Pomposo, Iñigo; Quiñones, Ileana; Carreiras, Manuel

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ABSTRACT Recent evidence suggests that damage to the language network triggers its functional reorganization. Yet, the spectro-temporal fingerprints of this plastic rearrangement and its relation to anatomical changes is less well understood. Here, we combined magnetoencephalographic recordings with a proxy measure of white matter to investigate oscillatory activity supporting language plasticity and its relation to structural reshaping. First, cortical dynamics were acquired in a group of healthy controls during object and action naming. Results showed segregated beta (13-28 Hz) power decreases in left ventral and dorsal pathways, in a time-window associated to lexico-semantic processing (~250-500 ms). Six patients with left tumors invading either ventral or dorsal regions performed the same naming task before and 3 months after surgery for tumor resection. When longitudinally comparing patients' responses we found beta compensation mimicking the category-based segregation showed by controls, with ventral and dorsal damage leading to selective compensation for object and action naming, respectively. At the structural level, all patients showed preoperative changes in white matter tracts possibly linked to plasticity triggered by tumor growth. Furthermore, in some patients, structural changes were also evident after surgery and showed associations with longitudinal changes in beta power lateralization toward the contralesional hemisphere. Overall, our findings support the existence of anatomo-functional dependencies in language reorganization and highlight the potential role of oscillatory markers in tracking longitudinal plasticity in brain tumor patients. By doing so, they provide valuable information for mapping preoperative and postoperative neural reshaping and plan surgical strategies to preserve language function and patient's quality of life.

Keywords: brain rhythms, brain tumors, language, magnetoencephalography, neuroplasticity

Human brain mapping (2021), Vol. 42, No. 6 (33368838) (9 citations)

Structural and Functional Imaging in Glioma Management (2021)

Brahimaj, Bledi C; Kochanski, Ryan B; Pearce, John J; Guryildirim, Melike; Gerard, Carter S; Kocak, Mehmet; Sani, Sepehr; Byrne, Richard W

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ABSTRACT The goal of glioma surgery is maximal safe resection in order to provide optimal tumor control and survival benefit to the patient. There are multiple imaging modalities beyond traditional contrast-enhanced magnetic resonance imaging (MRI) that have been incorporated into the preoperative workup of patients presenting with gliomas. The aim of these imaging modalities is to identify cortical and subcortical areas of eloquence, and their relationship to the lesion. In this article, multiple modalities are described with an emphasis on the underlying technology, clinical utilization, advantages, and disadvantages of each. functional MRI and its role in identifying hemispheric dominance and areas of language and motor are discussed. The nuances of magnetoencephalography and transcranial magnetic stimulation in localization of eloquent cortex are examined, as well as the role of diffusion tensor imaging in defining normal white matter tracts in glioma surgery. Lastly, we highlight the role of stimulated Raman spectroscopy in intraoperative histopathological diagnosis of tissue to guide tumor resection. Tumors may shift the normal arrangement of functional anatomy in the brain; thus, utilization of multiple modalities may be helpful in operative planning and patient counseling for successful surgery.

Keywords: Diffusion tensor imaging, Functional MRI, Glioma, Imaging, Low-grade glioma, Magnetoencephalography, Stimulated Raman microscopy, Transcranial magnetic stimulation

Neurosurgery (2021), Vol. 88, No. 2 (33313852) (4 citations)

Visual Mapping With Magnetoencephalography: An Update on the Current State of Clinical Research and Practice With Considerations for Clinical Practice Guidelines (2020)

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ABSTRACT Using visual evoked fields (VEFs) to differentiate healthy, normal brain function from dysfunctional cortex has been demonstrated to be both valid and reliable. Currently, VEFs are widely implemented to guide intracranial surgeries for epilepsy and brain tumors. There are several areas of possible future clinical use of VEFs, including early identification of disorders, such as multiple sclerosis, Parkinson's disease, stroke, and human immunodeficiency virus-associated neurocognitive disorders. These studies have suggested that VEFs could be used to study disease pathophysiology or as a biomarker for early identification of a disorder. The current clinical practice guidelines of the American Clinical Magnetoencephalography Society for VEFs are sufficient. At this time, VEFs should be used clinically

to identify visual cortex and potentially tailor surgical resections.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165231) (4 citations)

Association between tissue hypoxia, perfusion restrictions, and microvascular architecture alterations with lesion-induced impairment of neurovascular coupling (2022)

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ABSTRACT Functional magnetic resonance imaging (fMRI) has been mainly utilized for the preoperative localization of eloquent cortical areas. However, lesion-induced impairment of neurovascular coupling (NVC) in the lesion border zone may lead to false-negative fMRI results. The purpose of this study was to determine physiological factors impacting the NVC. Twenty patients suffering from brain lesions were preoperatively examined using multimodal neuroimaging including fMRI, magnetoencephalography (MEG) during language or sensorimotor tasks (depending on lesion location), and a novel physiologic MRI approach for the combined quantification of oxygen metabolism, perfusion state, and microvascular architecture. Congruence of brain activity patterns between fMRI and MEG were found in 13 patients. In contrast, we observed missing fMRI activity in perilesional cortex that demonstrated MEG activity in seven patients, which was interpreted as lesion-induced impairment of NVC. In these brain regions with impaired NVC, physiologic MRI revealed significant brain tissue hypoxia, as well as significantly decreased macro- and microvascular perfusion and microvascular architecture. We demonstrated that perilesional hypoxia with reduced vascular perfusion and architecture is associated with lesion-induced impairment of NVC. Our physiologic MRI approach is a clinically applicable method for preoperative risk assessment for the presence of false-negative fMRI results and may prevent severe postoperative functional deficits.

Keywords: Blood-oxygen-level-dependent contrast, functional magnetic resonance imaging, hypoxia, magnetoencephalography, neurovascular coupling

Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism (2022), Vol. 42, No. 3 (32787542) (3 citations)

A controlled clinical crossover trial of exercise training to improve cognition and neural communication in pediatric brain tumor survivors (2020)

Cox, Elizabeth; Bells, Sonya; Timmons, Brian W; Laughlin, Suzanne; Bouffet, Eric; de Medeiros, Cynthia; Beera, Kiran; Harasym, Diana; Mabbott, Donald J

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OBJECTIVE To assess the efficacy of aerobic exercise training to improve controlled attention, information processing speed and neural communication during increasing task load and rest in pediatric brain tumor survivors (PBTS) treated with cranial radiation.

METHODS Participants completed visual-motor Go and Go/No-Go tasks during magnetoencephalography recording prior to and following the completion of 12-weeks of exercise training. Exercise-related changes in response accuracy and visual-motor latency were evaluated with Linear Mixed models. The Phase Lag Index (PLI) was used to estimate functional connectivity during task performance and rest. Changes in PLI values after exercise training were assessed using Partial Least Squares analysis.

RESULTS Exercise training predicted sustained (12-weeks) improvement in response accuracy ($p<0.05$) during No-Go trials. Altered functional connectivity was detected in theta (4-7Hz) alpha (8-12Hz) and high gamma (60-100Hz) frequency bands ($p<0.001$) during Go and Go/No-Go trials. Significant changes in response latency and resting state connectivity were not detected.

CONCLUSION These findings support the efficacy of aerobic exercise to improve controlled attention and enhance functional mechanisms under increasing task load in participants.

SIGNIFICANCE It may be possible to harness the beneficial effects of exercise as therapy to promote cognitive recovery and enhance brain function in PBTS.

Keywords: Cognitive control, Exercise, Functional connectivity, Magnetoencephalography, Pediatric brain tumors

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 7 (32403066) (10 citations)

Presurgical Functional Mapping with Magnetoencephalography (2020)

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ABSTRACT Noninvasive functional brain imaging with magnetoencephalography (MEG) is regularly used to map the eloquent cortex associated with somatosensory, motor, auditory, visual, and language processing before a surgical resection to determine if the functional areas have been reorganized. Most tasks can also be performed in the pediatric population. To acquire an optimal MEG study for any of these modalities, the patient needs to be well rested and attending to the stimulation.

Keywords: Auditory evoked magnetic fields, Language evoked magnetic fields, Magnetoencephalography, Mapping, Motor evoked magnetic fields, Presurgical, Somatosensory evoked magnetic fields, Visual evoked magnetic fields

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336404) (4 citations)

Language Neuroplasticity in Brain Tumor Patients Revealed by Magnetoencephalography (2020)

Piai, Vitória; De Witte, Elke; Sierpowska, Joanna; Zheng, Xiaochen; Hinkley, Leighton B; Mizuiri, Danielle; Knight, Robert T; Berger, Mitchel S; Nagarajan, Srikantan S

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ABSTRACT Little is known about language impairment in brain tumor patients, especially in the presurgical phase. Impairment in this population may be missed because standardized tests fail to capture mild deficits. Additionally, neuroplasticity may also contribute to minimizing language impairments. We examined 14 presurgical patients with brain tumors in the language-dominant hemisphere using magnetoencephalography (MEG) while they performed a demanding picture-word interference task, that is, participants name pictures while ignoring distractor words. Brain tumor patients had behavioral picture-naming effects typically observed in healthy controls. The MEG responses also showed the expected pattern in its timing and amplitude modulation typical of controls, but with an altered spatial distribution of right hemisphere sources, in contrast to the classic left hemisphere source found in healthy individuals. This finding supports tumor-induced neural reorganization of language before surgery. Crucially, the use of electrophysiology allowed us to show the "same" neuronal response in terms of its timing and amplitude modulation in the right hemisphere, supporting the hypothesis that the processes performed by the right hemisphere following reorganization are similar in nature to those (previously) performed by the left hemisphere. We also identified one participant with a fast-growing tumor affecting large parts of critical language areas and underlying ventral and dorsal white matter tracts who showed a deviant pattern in behavior and in the MEG event-related responses. In conclusion, our results attest to the validity of using a demanding picture-naming task in presurgical patients and provide evidence for neuroplasticity, with the right hemisphere performing similar computations as the left hemisphere typically performs.

Journal of cognitive neuroscience (2020), Vol. 32, No. 8 (32286133) (7 citations)

The impact of high functional connectivity network hub resection on language task performance in adult low- and high-grade glioma (2020)

Lee, Anthony T; Faltermeier, Claire; Morshed, Ramin A; Young, Jacob S; Kakaizada, Sofia; Valdivia, Claudia; Findlay, Anne M; Tarapore, Phiroz E; Nagarajan, Srikantan S; Hervey-Jumper, Shawn L; Berger, Mitchel S

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OBJECTIVE Gliomas are intrinsic brain tumors with the hallmark of diffuse white matter infiltration, resulting in short- and long-range network dysfunction. Preoperative magnetoencephalography (MEG) can assist in maximizing the extent of resection while minimizing morbidity. While MEG has been validated in motor mapping, its role in speech mapping remains less well studied. The authors assessed how the resection of intraoperative electrical stimulation (IES)-negative, high functional connectivity (HFC) network sites, as identified by MEG, impacts language performance.

METHODS Resting-state, whole-brain MEG recordings were obtained from 26 patients who underwent perioperative language evaluation and glioma resection that was guided by awake language and IES mapping. The functional connectivity of an individual voxel was determined by the imaginary coherence between the index voxel and the rest of the brain, referenced to its contralesional pair. The percentage of resected HFC voxels was correlated with postoperative language outcomes in tasks of increasing complexity: text reading, 4-syllable repetition, picture naming, syntax (SYN), and auditory stimulus naming (AN).

RESULTS Overall, 70% of patients (14/20) in whom any HFC tissue was resected developed an early postoperative language deficit (mean 2.3 days, range 1-8 days), compared to 33% of patients (2/6) in whom no HFC tissue was resected ($p = 0.16$). When bifurcated by the amount of HFC tissue that was resected, 100% of patients (3/3) with an HFC resection > 25% displayed deficits in AN, compared to 30% of patients (6/20) with an HFC resection < 25% ($p = 0.04$). Furthermore, there was a linear correlation between the severity of AN and SYN decline with percentage of HFC sites resected ($p = 0.02$ and $p = 0.04$, respectively). By 2.2 months postoperatively (range 1-6 months), the correlation between HFC resection and both AN and SYN decline had resolved ($p = 0.94$ and $p = 1.00$, respectively) in all patients (9/9) except two who experienced early postoperative tumor progression or stroke involving inferior frontooccipital fasciculus.

CONCLUSIONS Imaginary coherence measures of functional connectivity using MEG are able to identify HFC network sites within and around low- and high-grade gliomas. Removal of IES-negative HFC sites results in early transient postoperative decline in AN and SYN, which resolved by 3 months in all patients without stroke or early tumor progression. Measures of functional connectivity may therefore be a useful means of counseling patients about postoperative risk and assist with preoperative surgical planning.

Keywords: functional connectivity, glioblastoma, high-grade glioma, language, low-grade glioma, magnetoencephalography, oncology, speech

Journal of neurosurgery (2020), Vol. 134, No. 3 (32244221) (13 citations)

Accuracy analysis of fMRI and MEG activations determined by intraoperative mapping (2020)

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OBJECTIVE By looking at how the accuracy of preoperative brain mapping methods vary according to differences in the distance from the activation clusters used for the analysis, the present study aimed to elucidate how preoperative functional neuroimaging may be used in such a way that maximizes the mapping accuracy.

METHODS The eloquent function of 19 patients with a brain tumor or cavernoma was mapped prior to resection with both functional MRI (fMRI) and magnetoencephalography (MEG). The mapping results were then validated using direct cortical stimulation mapping performed immediately after craniotomy and prior to resection. The subset of patients with equivalent MEG and fMRI tasks performed for motor ($n = 14$) and language ($n = 12$) were evaluated as both individual and combined predictions. Furthermore, the distance resulting in the maximum accuracy, as evaluated by the J statistic, was determined by plotting the sensitivities and specificities against a linearly increasing distance threshold.

RESULTS fMRI showed a maximum mapping accuracy at 5 mm for both motor and language mapping. MEG showed a maximum mapping accuracy at 40 mm for motor and 15 mm for language mapping. At the standard 10-mm distance used in the literature, MEG showed a greater specificity than fMRI for both motor and language mapping but a lower sensitivity for motor mapping. Combining MEG and fMRI showed a maximum accuracy at 15 mm and 5 mm-MEG and fMRI distances, respectively-for motor mapping and at a 10-mm distance for both MEG and fMRI for language mapping. For motor mapping, combining MEG and fMRI at the optimal distances resulted in a greater accuracy than the maximum accuracy of the individual predictions.

CONCLUSIONS This study demonstrates that the accuracy of language and motor mapping for both fMRI and MEG is heavily dependent on the distance threshold

used in the analysis. Furthermore, combining MEG and fMRI showed the potential for increased motor mapping accuracy compared to when using the modalities separately.Clinical trial registration no.: NCT01535430 (clinicaltrials.gov).

Keywords: BVS = blood vessel segmentation, DCS = direct cortical stimulation, MEG, MEG = magnetoencephalography, T1W = T1-weighted, brain mapping, brain tumor, eloquent, fMRI, fMRI = functional MRI

Neurosurgical focus (2020), Vol. 48, No. 2 (32006951) (12 citations)

Postoperative oscillatory brain activity as an add-on prognostic marker in diffuse glioma (2020)

Belgers, Vera; Numan, Tianne; Kulik, Shanna D; Hillebrand, Arjan; de Witt Hamer, Philip C; Geurts, Jeroen J G; Reijneveld, Jaap C; Wesseling, Pieter; Klein, Martin; Derks, Jolanda; Douw, Linda

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INTRODUCTION Progression-free survival (PFS) in glioma patients varies widely, even when stratifying for known predictors (i.e. age, molecular tumor subtype, presence of epilepsy, tumor grade and Karnofsky performance status). Neuronal activity has been shown to accelerate tumor growth in an animal model, suggesting that brain activity may be valuable as a PFS predictor. We investigated whether postoperative oscillatory brain activity, assessed by resting-state magnetoencephalography is of additional value when predicting PFS in glioma patients.

METHODS We included 27 patients with grade II-IV gliomas. Each patient's oscillatory brain activity was estimated by calculating broadband power (0.5-48 Hz) in 56 epochs of 3.27 s and averaged over 78 cortical regions of the Automated Anatomical Labeling atlas. Cox proportional hazard analysis was performed to test the predictive value of broadband power towards PFS, adjusting for known predictors by backward elimination.

RESULTS Higher broadband power predicted shorter PFS after adjusting for known prognostic factors ($n = 27$; HR 2.56 (95% confidence interval (CI) 1.15-5.70); $p = 0.022$). Post-hoc univariate analysis showed that higher broadband power also predicted shorter overall survival (OS; $n = 38$; HR 1.88 (95% CI 1.00-3.54); $p = 0.038$).

CONCLUSIONS Our findings suggest that postoperative broadband power is of additional value in predicting PFS beyond already known predictors.

Keywords: Beamforming, Glioma, Magnetoencephalography (MEG), Overall survival, Progression-free survival

Journal of neuro-oncology (2020), Vol. 147, No. 1 (31953611) (6 citations)

Spatiotemporal dynamics of postoperative functional plasticity in patients with brain tumors in language areas (2020)

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ABSTRACT Postoperative functional neuroimaging provides a unique opportunity to investigate the neural mechanisms that facilitate language network reorganization. Previous studies in patients with low grade gliomas (LGGs) in language areas suggest that postoperative recovery is likely due to functional neuroplasticity in peritumoral and contra-tumoral healthy regions, but have attributed varying degrees of importance to specific regions. In this study, we used Magnetoencephalography (MEG) to investigate functional connectivity changes in peritumoral and contra-tumoral regions after brain tumor resection. MEG recordings of cortical activity during resting-state were obtained from 12 patients with LGGs in left-hemisphere language brain areas. MEG data were recorded before (Pre session), and 3 (Post_1 session) and 6 (Post_2 session) months after awake craniotomy. For each MEG session, we measured the functional connectivity of the peritumoral and contra-tumoral regions to the rest of the brain across the 1-100 Hz frequency band. We found that functional connectivity in the Post_1 and Post_2 sessions was higher than in the Pre session only in peritumoral regions and within the alpha frequency band. Functional connectivity in peritumoral regions did not differ between the Post_1 and Post_2 sessions. Alpha connectivity enhancement in peritumoral regions was observed in all patients regardless of the LGG location. Together, these results suggest that postoperative language functional reorganization occurs in peritumoral regions regardless of the location of the tumor and mostly develops within 3 months after surgery.

Keywords: Functional connectivity, Functional reorganization, Language networks, Low-grade glioma, Magnetoencephalography

Brain and language (2020), Vol. 202 (31931399) (13 citations)

Refined Functional Magnetic Resonance Imaging and Magnetoencephalography Mapping Reveals Reorganization in Language-Relevant Areas of Lesioned Brains (2020)

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BACKGROUND Neurosurgical decisions regarding interventions close to brain areas with language-related functions remain highly challenging because of the risk of postoperative dysfunction. To minimize these risks, improvements in the preoperative mapping of language-related regions are required, especially as space-occupying lesions often lead to altered cortical topography and language area reorganization.

METHODS The degree of deviation and language area reorganization were investigated in 26 functional magnetic resonance imaging- and magnetoenceph-

alography-dissociable cortical sub-areas displaying language-related activations in each of 18 patients with brain lesions and 3 healthy volunteers (during visual language tasks).

RESULTS Both modalities showed good congruency of the language areas. The mean spatial distance of the centroids and maxima was 9.06 mm and 10.58 mm, respectively, allowing us to define more specific anatomical positions. Postoperatively, language abilities increased in 11% (2 of 18) of the patients, remained unchanged in 83% (15 of 18) of the patients, and decreased in 6% (1 of 18) of the patients, respectively. Signs of language function reorganization detected on both functional magnetic resonance imaging and magnetoencephalography were present in 29% (5 of 17) of the patients. Attenuation of neurovascular coupling was found postoperatively in 17% (3 of 18) of the patients. Monohemispheric language processing cannot be assumed always in patients with brain lesions.

CONCLUSIONS The more detailed subdivision of language-relevant brain areas shown in this study can help to achieve more radical tumor resection without postoperative language deficits.

Keywords: Brain tumor, Broca, Language, MEG, Reorganization, Wernicke, fMRI

World neurosurgery (2020), Vol. 136 (31606506) (4 citations)

Early visual alterations in individuals at-risk of Alzheimer's disease: a multidisciplinary approach (2023)

López-Cuenca, Inés; Nebreda, Alberto; García-Colomo, Alejandra; Salobrar-García, Elena; de Frutos-Lucas, Jaisalmer; Bruña, Ricardo; Ramírez, Ana I; Ramirez-Toraño, Federico; Salazar, Juan J; Barabash, Ana; Gil, Pedro; Maestú, Fernando; Ramírez, José M; de Hoz, Rosa

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BACKGROUND The earliest pathological features of Alzheimer's disease (AD) appear decades before the clinical symptoms. The pathology affects the brain and the eye, leading to retinal structural changes and functional visual alterations. Healthy individuals at high risk of developing AD present alterations in these ophthalmological measures, as well as in resting-state electrophysiological activity. However, it is unknown whether the ophthalmological alterations are related to the visual-related electrophysiological activity. Elucidating this relationship is paramount to understand the mechanisms underlying the early deterioration of the system and an important step in assessing the suitability of these measures as early biomarkers of disease.

METHODS In total, 144 healthy subjects: 105 with family history of AD and 39 without, underwent ophthalmologic analysis, magnetoencephalography recording, and genotyping. A subdivision was made to compare groups with less demographic and more risk differences: 28 high-risk subjects (relatives/APOE 4+) and 16 low-risk (non-relatives/APOE 4-). Differences in visual acuity, contrast sensitivity, and macular thickness were evaluated. Correlations between each variable and visual-related electrophysiological measures (M100 latency and time-frequency power) were calculated for each group.

RESULTS High-risk groups showed increased visual acuity. Visual acuity was also related to a lower M100 latency and a greater power time-frequency cluster in the high-risk group. Low-risk groups did not show this relationship. High-risk groups presented trends towards a greater contrast sensitivity that did not remain significant after correction for multiple comparisons. The highest-risk group showed trends towards the thinning of the inner plexiform and inner nuclear layers that did not remain significant after correction. The correlation between contrast sensitivity and macular thickness, and the electrophysiological measures were not significant after correction. The difference between the high- and low- risk groups correlations was no significant.

CONCLUSIONS To our knowledge, this paper is the first of its kind, assessing the relationship between ophthalmological and electrophysiological measures in healthy subjects at distinct levels of risk of AD. The results are novel and unexpected, showing an increase in visual acuity among high-risk subjects, who also exhibit a relationship between this measure and visual-related electrophysiological activity. These results have not been previously explored and could constitute a useful object of research as biomarkers for early detection and the evaluation of potential interventions' effectiveness.

Keywords: Alzheimer’s disease, At risk for AD, Magneto-encephalography, Optical coherence tomography, Visual function

Alzheimer's research & therapy (2023), Vol. 15, No. 1 (36694201) (0 citations)

Oscillatory markers of neuroHIV-related cognitive impairment and Alzheimer's disease during attentional interference processing (2023)

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ABSTRACT People with HIV (PWH) frequently experience mild cognitive decline, which is typically attributed to HIV-associated neurocognitive disorder (HAND). However, such declines could also be a sign of early Alzheimer's disease (AD) in older PWH. Distinguishing these two pathologies in PWH is exceedingly difficult, as there is a major knowledge gap regarding their neural and neuropsychological bases. In the current study, we begin to address this knowledge gap by recording magnetoencephalography (MEG) during a flanker interference task in 31 biomarker-confirmed patients on the AD spectrum (ADS), 25 older participants with HAND, and 31 cognitively-normal controls. MEG data was examined in the time-frequency domain using a data-driven approach. Our results indicated that the clinical groups (ADS/HAND) performed significantly worse than controls on the task and exhibited aberrations in interference-related theta and alpha oscillations, some of which were disease-specific. Specifically, patients (ADS/HAND) exhibited weaker interference activity in frontoparietal and cingulate cortices compared to controls, while the ADS group exhibited stronger theta interference than those with HAND in frontoparietal, occipital, and temporal cortices. These results reveal overlapping and distinct patterns of neurophysiological alterations among those with ADS and HAND in attentional processing centers and suggest the existence of unique oscillatory markers of each condition.

Keywords: MEG, magnetoencephalography, neuroHIV, oscillations, top-down

Aging (2023), Vol. 15, No. 2 (36656738) (0 citations)

New Therapeutics in Alzheimer's Disease Longitudinal Cohort study (NTAD): study protocol (2022)

Lanskey, Juliette Helene; Kocagoncu, Ece; Quinn, Andrew J; Cheng, Yun-Ju; Karadag, Melek; Pitt, Jemma; Lowe, Stephen; Perkinton, Michael; Raymont, Vanessa; Singh, Krish D; Woolrich, Mark; Nobre, Anna C; Henson, Richard N; Rowe, James B; NTAD study group

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INTRODUCTION With the pressing need to develop treatments that slow or stop the progression of Alzheimer's disease, new tools are needed to reduce clinical trial duration and validate new targets for human therapeutics. Such tools could be derived from neurophysiological measurements of disease.

METHODS AND ANALYSIS The New Therapeutics in Alzheimer's Disease study (NTAD) aims to identify a biomarker set from magneto/electroencephalography that is sensitive to disease and progression over 1 year. The study will recruit 100 people with amyloid-positive mild cognitive impairment or early-stage Alzheimer's disease and 30 healthy controls aged between 50 and 85 years. Measurements of the clinical, cognitive and imaging data (magnetoencephalography, electroencephalography and MRI) of all participants will be taken at baseline. These measurements will be repeated after approximately 1 year on participants with Alzheimer's disease or mild cognitive impairment, and clinical and cognitive assessment of these participants will be repeated again after approximately 2 years. To assess reliability of magneto/electroencephalographic changes, a subset of 30 participants with mild cognitive impairment or early-stage Alzheimer's disease will also undergo repeat magneto/electroencephalography 2 weeks after baseline. Baseline and longitudinal changes in neurophysiology are the primary analyses of interest. Additional outputs will include atrophy and cognitive change and estimated numbers needed to treat each arm of simulated clinical trials of a future disease-modifying therapy.

ETHICS AND DATA STATEMENT The study has received a favourable opinion from the East of England Cambridge Central Research Ethics Committee (REC reference 18/EE/0042). Results will be disseminated through internal reports, peer-reviewed scientific journals, conference presentations, website publication, submission to regulatory authorities and other publications. Data will be made available via the Dementias Platform UK Data Portal on completion of initial analyses by the NTAD study group.

Keywords: Dementia, NEUROLOGY, NEUROPHYSIOLOGY, Neurophysiology, Protocols & guidelines, RADIOLOGY & IMAGING

BMJ open (2022), Vol. 12, No. 12 (36521898) (0 citations)

The neurophysiological effect of NMDA-R antagonism of frontotemporal lobar degeneration is conditional on individual GABA concentration (2022)

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ABSTRACT There is a pressing need to accelerate therapeutic strategies against the syndromes caused by frontotemporal lobar degeneration, including symptomatic treatments. One approach is for experimental medicine, coupling neurophysiological studies of the mechanisms of disease with pharmacological interventions aimed at restoring neurochemical deficits. Here we consider the role of glutamatergic deficits and their potential as targets for treatment. We performed a double-blind placebo-controlled crossover pharmacomagnetoencephalography study in 20 people with symptomatic frontotemporal lobar degeneration (10 behavioural variant frontotemporal dementia, 10 progressive supranuclear palsy) and 19 healthy age- and gender-matched controls. Both magnetoencephalography sessions recorded a roving auditory oddball paradigm: on placebo or following 10 mg memantine, an uncompetitive NMDA-receptor antagonist. Ultra-

high-field magnetic resonance spectroscopy confirmed lower concentrations of GABA in the right inferior frontal gyrus of people with frontotemporal lobar degeneration. While memantine showed a subtle effect on early-auditory processing in patients, there was no significant main effect of memantine on the magnitude of the mismatch negativity (MMN) response in the right frontotemporal cortex in patients or controls. However, the change in the right auditory cortex MMN response to memantine (vs. placebo) in patients correlated with individuals' prefrontal GABA concentration. There was no moderating effect of glutamate concentration or cortical atrophy. This proof-of-concept study demonstrates the potential for baseline dependency in the pharmacological restoration of neurotransmitter deficits to influence cognitive neurophysiology in neurodegenerative disease. With changes to multiple neurotransmitters in frontotemporal lobar degeneration, we suggest that individuals' balance of excitation and inhibition may determine drug efficacy, with implications for drug selection and patient stratification in future clinical trials.

Translational psychiatry (2022), Vol. 12, No. 1 (36030249) (0 citations)

A multiscale brain network model links Alzheimer's disease-mediated neuronal hyperactivity to large-scale oscillatory slowing (2022)

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BACKGROUND Neuronal hyperexcitability and inhibitory interneuron dysfunction are frequently observed in preclinical animal models of Alzheimer's disease (AD). This study investigates whether these microscale abnormalities explain characteristic large-scale magnetoencephalography (MEG) activity in human early-stage AD patients.

METHODS To simulate spontaneous electrophysiological activity, we used a whole-brain computational network model comprised of 78 neural masses coupled according to human structural brain topology. We modified relevant model parameters to simulate six literature-based cellular scenarios of AD and compare them to one healthy and six contrast (non-AD-like) scenarios. The parameters include excitability, postsynaptic potentials, and coupling strength of excitatory and inhibitory neuronal populations. Whole-brain spike density and spectral power analyses of the simulated data reveal mechanisms of neuronal hyperactivity that lead to oscillatory changes similar to those observed in MEG data of 18 human prodromal AD patients compared to 18 age-matched subjects with subjective cognitive decline.

RESULTS All but one of the AD-like scenarios showed higher spike density levels, and all but one of these scenarios had a lower peak frequency, higher spectral power in slower (theta, 4-8Hz) frequencies, and greater total power. Non-AD-like scenarios showed opposite patterns mainly, including reduced spike density and faster oscillatory activity. Human AD patients showed oscillatory slowing (i.e., higher relative power in the theta band mainly), a trend for lower peak frequency and higher total power compared to controls. Combining model and human data, the findings indicate that neuronal hyperactivity can lead to oscillatory slowing, likely due to hyperexcitation (by hyperexcitability of pyramidal neurons or greater long-range excitatory coupling) and/or disinhibition (by reduced excitability of inhibitory interneurons or weaker local inhibitory coupling strength) in early AD.

CONCLUSIONS Using a computational brain network model, we link findings from different scales and models and support the hypothesis of early-stage neuronal hyperactivity underlying E/I imbalance and whole-brain network dysfunction in prodromal AD.

Keywords: Alzheimer's disease, Computational modeling, Hyperexcitability, MEG, Neural mass models, Neuronal network, Oscillatory slowing

Alzheimer's research & therapy (2022), Vol. 14, No. 1 (35879779) (0 citations)

Functional changes in brain oscillations in dementia: a review (2023)

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ABSTRACT A growing body of evidence indicates that several characteristics of electroencephalography (EEG) and magnetoencephalography (MEG) play a functional role in cognition and could be linked to the progression of cognitive decline in some neurological diseases such as dementia. The present paper reviews previous studies investigating changes in brain oscillations associated to the most common types of dementia, namely Alzheimer's disease (AD), frontotemporal degeneration (FTD), and vascular dementia (VaD), with the aim of identifying pathology-specific patterns of alterations and supporting differential diagnosis in clinical practice. The included studies analysed changes in frequency power, functional connectivity, and event-related potentials, as well as the relationship between electrophysiological changes and cognitive deficits. Current evidence suggests that an increase in slow wave activity (i.e., theta and delta) as well as a general reduction in the power of faster frequency bands (i.e., alpha and beta) characterizes AD, VaD, and FTD. Additionally, compared to healthy controls, AD exhibits alteration in latencies and amplitudes of the most common event related potentials. In the reviewed studies, these changes generally correlate with performances in many cognitive tests. In conclusion, particularly in AD, neurophysiological changes can be reliable early markers of dementia.

Keywords: Alzheimer disease, ERP, brain oscillations, frontotemporal dementia, vascular dementia

Reviews in the neurosciences (2023), Vol. 34, No. 1 (35724724) (0 citations)

A multi-site, multi-participant magnetoencephalography resting-state dataset to study dementia: The BioFIND dataset (2022)

Vaghari, Delshad; Bruna, Ricardo; Hughes, Laura E; Nesbitt, David; Tibon, Roni; Rowe, James B; Maestu, Fernando; Henson, Richard N

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ABSTRACT Early detection of Alzheimer's Disease (AD) is vital to reduce the burden of dementia and for developing effective treatments. Neuroimaging can detect early brain changes, such as hippocampal atrophy in Mild Cognitive Impairment (MCI), a prodromal state of AD. However, selecting the most informative imaging features by machine-learning requires many cases. While large publically-available datasets of people with dementia or prodromal disease exist for Magnetic Resonance Imaging (MRI), comparable datasets are missing for Magnetoencephalography (MEG). MEG offers advantages in its millisecond resolution, revealing physiological changes in brain oscillations or connectivity before structural changes are evident with MRI.

We introduce a MEG dataset with 324 individuals: patients with MCI and healthy controls. Their brain activity was recorded while resting with eyes closed, using a 306-channel MEG scanner at one of two sites (Madrid or Cambridge), enabling tests of generalization across sites. A T1-weighted MRI is provided to assist source localisation. The MEG and MRI data are formatted according to international BIDS standards and analysed freely on the DPUK platform (https://portal.dementiasplatform.uk/Apply). Here, we describe this dataset in detail, report some example (benchmark) analyses, and consider its limitations and future directions.

NeuroImage (2022), Vol. 258 (35660461) (1 citation)

Altered excitatory and inhibitory neuronal subpopulation parameters are distinctly associated with tau and amyloid in Alzheimer's disease (2022)

Ranasinghe, Kamalini G; Verma, Parul; Cai, Chang; Xie, Xihe; Kudo, Kiwamu; Gao, Xiao; Lerner, Hannah; Mizuiri, Danielle; Strom, Amelia; Iaccarino, Leonardo; La Joie, Renaud; Miller, Bruce L; Gorno-Tempini, Maria Luisa; Rankin, Katherine P; Jagust, William J; Vossel, Keith; Rabinovici, Gil D; Raj, Ashish; Nagarajan, Srikantan S

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BACKGROUND Neuronal- and circuit-level abnormalities of excitation and inhibition are shown to be associated with tau and amyloid-beta (Aβ) in preclinical models of Alzheimer's disease (AD). These relationships remain poorly understood in patients with AD.

METHODS Using empirical spectra from magnetoencephalography and computational modeling (neural mass model), we examined excitatory and inhibitory parameters of neuronal subpopulations and investigated their specific associations to regional tau and Aβ, measured by positron emission tomography, in patients with AD.

RESULTS Patients with AD showed abnormal excitatory and inhibitory time-constants and neural gains compared to age-matched controls. Increased excitatory time-constants distinctly correlated with higher tau depositions while increased inhibitory time-constants distinctly correlated with higher Aβ depositions.

CONCLUSIONS Our results provide critical insights about potential mechanistic links between abnormal neural oscillations and cellular correlates of impaired excitatory and inhibitory synaptic functions associated with tau and Aβ in patients with AD.

FUNDING This study was supported by the National Institutes of Health grants: K08AG058749 (KGR), F32AG050434-01A1 (KGR), K23 AG038357 (KAV), P50 AG023501, P01 AG19724 (BLM), P50-AG023501 (BLM and GDR), R01 AG045611 (GDR); AG034570, AG062542 (WJ); NS100440 (SSN), DC176960 (SSN), DC017091 (SSN), AG062196 (SSN); a grant from John Douglas French Alzheimer's Foundation (KAV); grants from Larry L. Hillblom Foundation: 2015-A-034-FEL (KGR), 2019-A-013-SUP (KGR); grants from the Alzheimer's Association: AARG-21-849773 (KGR); PCTRB-13-288476 (KAV), and made possible by Part the CloudTM (ETAC-09-133596); a grant from Tau Consortium (GDR and WJJ), and a gift from the S. D. Bechtel Jr. Foundation.

Keywords: Alzheimer's disease, human, magnetoencephalogrpahy, medicine, neural mass model, neuroscience, tau-PET

eLife (2022), Vol. 11 (35616532) (5 citations)

Prominent gamma band activity during visual motion perception in early-stage Alzheimer's disease (2022)

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INTRODUCTION Alzheimer's disease (AD) affects multiple neural pathways and regions, resulting in various visual impairments such as motion perception. Generally, gamma-band activities during visual motion perception have been thought to reflect ongoing cognitive processes. Nevertheless, few studies have specifically examined induced gamma band activity during visual motion perception in AD patients. Therefore, after performing magnetoencephalography (MEG) recording during apparent motion (AM) stimulation for the left hemi-visual field in patients diagnosed as having AD in the early stage, we compared the results with findings of cognitive performance.

METHODS Seventeen AD patients in the early stage and 17 controls matched for age, sex, and educational attainment participated in this study. For each participant, memory performance was assessed with the Mini-Mental State Examination (MMSE) and the Wechsler Memory Scale-Revised (WMS-R). For MEG analysis, we examined power changes induced in a higher frequency range (20-100 Hz) after AM stimuli.

RESULTS The power of induced gamma band activities was significantly higher in AD patients. The power of induced gamma band activities was associated with higher performance on both MMSE and WMS-R tests for attention and concentration in AD patients.

CONCLUSIONS Given that neuronal dysfunction in AD is associated with excitotoxic neurodegeneration, and given that subsequent development of compensatory inhibitory mechanisms also contributes to pathology in AD patients, elevated gamma band oscillations might reflect an imbalance of inhibitory and excitatory activity in AD patients. Moreover, positive correlation between induced gamma activity and cognitive performance might signify a compensating mechanism of inhibitory neurons which preserve the pyramidal neuron from excitotoxicity in a posterior association area.

PloS one (2022), Vol. 17, No. 4 (35436287) (0 citations)

Oscillatory Activity of the Hippocampus in Prodromal Alzheimer's Disease: A Source-Space Magnetoencephalography Study (2022)

Luppi, Janne J; Schoonhoven, Deborah N; van Nifterick, Anne M; Gouw, Alida A; Hillebrand, Arjan; Scheltens, Philip; Stam, Cornelis J; de Haan, Willem

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BACKGROUND In Alzheimer's disease (AD), oscillatory activity of the human brain slows down. However, oscillatory slowing varies between individuals, particularly in prodromal AD. Cortical oscillatory changes have shown suboptimal accuracy as diagnostic markers. We speculated that focusing on the hippocampus might prove more successful, particularly using magnetoencephalography (MEG) for capturing subcortical oscillatory activity.

OBJECTIVE We explored MEG-based detection of hippocampal oscillatory abnormalities in prodromal AD patients.

METHODS We acquired resting-state MEG data of 18 AD dementia patients, 18 amyloid-β-positive amnestic mild cognitive impairment (MCI, prodromal AD) patients, and 18 amyloid-β-negative persons with subjective cognitive decline (SCD). Oscillatory activity in 78 cortical regions and both hippocampi was reconstructed using beamforming. Between-group and hippocampal-cortical differences in spectral power

were assessed. Classification accuracy was explored using ROC curves.

RESULTS The MCI group showed intermediate power values between SCD and AD, except for the alpha range, where it was higher than both ($p<0.05$ and $p<0.001$). The largest differences between MCI and SCD were in the theta band, with higher power in MCI ($p<0.01$). The hippocampi showed several unique group differences, such as higher power in the higher alpha band in MCI compared to SCD ($p<0.05$). Classification accuracy (MCI versus SCD) was best for absolute theta band power in the right hippocampus (AUC=0.87).

CONCLUSION In this MEG study, we detected oscillatory abnormalities of the hippocampi in prodromal AD patients. Moreover, hippocampus-based classification performed better than cortex-based classification. We conclude that a focus on hippocampal MEG may improve early detection of AD-related neuronal dysfunction.

Keywords: Alzheimer's disease, dementia, hippocampus, magnetoencephalography, mild cognitive impairment, spectral analysis

Journal of Alzheimer's disease: JAD (2022), Vol. 87, No. 1 (35311705) (0 citations)

Causal Evidence for the Multiple Demand Network in Change Detection: Auditory Mismatch Magnetoencephalography across Focal Neurodegenerative Diseases (2022)

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ABSTRACT The multiple demand (MD) system is a network of fronto-parietal brain regions active during the organization and control of diverse cognitive operations. It has been argued that this activation may be a nonspecific signal of task difficulty. However, here we provide convergent evidence for a causal role for the MD network in the "simple task" of automatic auditory change detection, through the impairment of top-down control mechanisms. We employ independent structure-function mapping, dynamic causal modeling (DCM), and frequency-resolved functional connectivity analyses of MRI and magnetoencephalography (MEG) from 75 mixed-sex human patients across four neurodegenerative syndromes [behavioral variant fronto-temporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), posterior cortical atrophy (PCA), and Alzheimer's disease mild cognitive impairment with positive amyloid imaging (ADMCI)] and 48 age-matched controls. We show that atrophy of any MD node is sufficient to impair auditory neurophysiological response to change in frequency, location, intensity, continuity, or duration. There was no similar association with atrophy of the cingulo-opercular, salience or language networks, or with global atrophy. MD regions displayed increased functional but decreased effective connectivity as a function of neurodegeneration, suggesting partially effective compensation. Overall, we show that damage to any of the nodes of the MD network is sufficient to impair top-down control of sensation, providing a common mechanism for impaired change detection across dementia syndromes.SIGNIFICANCE STATEMENT Previous evidence for fronto-parietal networks controlling perception is largely associative and may be confounded by task difficulty. Here, we use a preattentive measure of automatic auditory change detection [mismatch negativity (MMN) magnetoencephalography (MEG)] to show that neurodegeneration in any frontal or parietal multiple demand (MD) node impairs primary auditory cortex (A1) neurophysiological response to change through top-down mechanisms. This explains why the

impaired ability to respond to change is a core feature across dementias, and other conditions driven by brain network dysfunction, such as schizophrenia. It validates theoretical frameworks in which neurodegenerating networks upregulate connectivity as partially effective compensation. The significance extends beyond network science and dementia, in its construct validation of dynamic causal modeling (DCM), and human confirmation of frequency-resolved analyses of animal neurodegeneration models.

Keywords: Alzheimer's disease, bvFTD, dementia, dynamic causal modeling, mismatch negativity, multiple demand

The Journal of neuroscience: the official journal of the Society for Neuroscience (2022), Vol. 42, No. 15 (35260433) (1 citation)

Late combination shows that MEG adds to MRI in classifying MCI versus controls (2022)

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ABSTRACT Early detection of Alzheimer's disease (AD) is essential for developing effective treatments. Neuroimaging techniques like Magnetic Resonance Imaging (MRI) have the potential to detect brain changes before symptoms emerge. Structural MRI can detect atrophy related to AD, but it is possible that functional changes are observed even earlier. We therefore examined the potential of Magnetoencephalography (MEG) to detect differences in functional brain activity in people with Mild Cognitive Impairment (MCI) - a state at risk of early AD. We introduce a framework for multimodal combination to ask whether MEG data from a resting-state provides complementary information beyond structural MRI data in the classification of MCI versus controls. More specifically, we used multi-kernel learning of support vector machines to classify 163 MCI cases versus 144 healthy elderly controls from the BioFIND dataset. When using the covariance of planar gradiometer data in the low Gamma range (30-48 Hz), we found that adding a MEG kernel improved classification accuracy above kernels that captured several potential confounds (e.g., age, education, time-of-day, head motion). However, accuracy using MEG alone (68%) was worse than MRI alone (71%). When simply concatenating (normalized) features from MEG and MRI into one kernel (Early combination), there was no advantage of combining MEG with MRI versus MRI alone. When combining kernels of modality-specific features (Intermediate combination), there was an improvement in multimodal classification to 74%. The biggest multimodal improvement however occurred when we combined kernels from the predictions of modality-specific classifiers (Late combination), which achieved 77% accuracy (a reliable improvement in terms of permutation testing). We also explored other MEG features, such as the variance versus covariance of magnetometer versus planar gradiometer data within each of 6 frequency bands (delta, theta, alpha, beta, low gamma, or high gamma), and found that they generally provided complementary information for classification above MRI. We conclude that MEG can improve on the MRI-based classification of MCI.

Keywords: Alzheimer's disease, MEG, Machine learning, Mild cognitive impairment, Multimodal integration, Structural MRI

NeuroImage (2022), Vol. 252 (35247546) (0 citations)

Sensitive and reproducible MEG resting-state metrics of functional connectivity in Alzheimer's disease (2022)

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BACKGROUND Analysis of functional brain networks in Alzheimer's disease (AD) has been hampered by a lack of reproducible, yet valid metrics of functional connectivity (FC). This study aimed to assess both the sensitivity and reproducibility of the corrected amplitude envelope correlation (AEC-c) and phase lag index (PLI), two metrics of FC that are insensitive to the effects of volume conduction and field spread, in two separate cohorts of patients with dementia due to AD versus healthy elderly controls.

METHODS Subjects with a clinical diagnosis of AD dementia with biomarker proof, and a control group of subjective cognitive decline (SCD), underwent two 5-min resting-state MEG recordings. Data consisted of a test (AD = 28; SCD = 29) and validation (AD = 29; SCD = 27) cohort. Time-series were estimated for 90 regions of interest (ROIs) in the automated anatomical labelling (AAL) atlas. For each of five canonical frequency bands, the AEC-c and PLI were calculated between all 90 ROIs, and connections were averaged per ROI. General linear models were constructed to compare the global FC differences between the groups, assess the reproducibility, and evaluate the effects of age and relative power. Reproducibility of the regional FC differences was assessed using the Mann-Whitney U tests, with correction for multiple testing using the false discovery rate (FDR).

RESULTS The AEC-c showed significantly and reproducibly lower global FC for the AD group compared to SCD, in the alpha (8-13 Hz) and beta (13-30 Hz) bands, while the PLI revealed reproducibly lower FC for the AD group in the delta (0.5-4 Hz) band and higher FC for the theta (4-8 Hz) band. Regionally, the beta band AEC-c showed reproducibility for almost all ROIs (except for 13 ROIs in the frontal and temporal lobes). For the other bands, the AEC-c and PLI did not show regional reproducibility after FDR correction. The theta band PLI was susceptible to the effect of relative power.

CONCLUSION For MEG, the AEC-c is a sensitive and reproducible metric, able to distinguish FC differences between patients with AD dementia and cognitively healthy controls. These two measures likely reflect different aspects of neural activity and show differential sensitivity to changes in neural dynamics.

Keywords: Alzheimer's disease, Functional connectivity, Magnetoencephalography, Reproducibility, Sensitivity, Subjective cognitive decline

Alzheimer's research & therapy (2022), Vol. 14, No. 1 (35219327) (0 citations)

Cortical and subcortical changes in resting-state neuronal activity and connectivity in early symptomatic ALS and advanced frontotemporal dementia (2022)

Govaarts, Rosanne; Beeldman, Emma; Fraschini, Matteo; Griffa, Alessandra; Engels, Marjolein M A; van Es, Michael A; Veldink, Jan H; van den Berg, Leonard H; van der Kooi, Anneke J; Pijnenburg, Yolande A L; de Visser, Marianne; Stam, Cornelis J; Raaphorst, Joost; Hillebrand, Arjan

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ABSTRACT The objective of this study was to examine if patterns of resting-state brain activity and functional

connectivity in cortical and subcortical regions in patients with early symptomatic amyotrophic lateral sclerosis (ALS) resemble those of behavioural variant frontotemporal dementia (bvFTD). In a cross-sectional design, eyes-closed resting-state magnetoencephalography (MEG) data of 34 ALS patients, 18 bvFTD patients and 18 age- and gender-matched healthy controls (HCs) were projected to source-space using an atlas-based beamformer. Group differences in peak frequency, band-specific oscillatory activity and functional connectivity (corrected amplitude envelope correlation) in 78 cortical regions and 12 subcortical regions were determined. False discovery rate was used to correct for multiple comparisons. BvFTD patients, as compared to ALS and HCs, showed lower relative beta power in parietal, occipital, temporal and nearly all subcortical regions. Compared to HCs, patients with ALS and patients with bvFTD had a higher delta (0.5-4 Hz) and gamma (30-48 Hz) band resting-state functional connectivity in a high number of overlapping regions in the frontal lobe and in limbic and subcortical regions. Higher delta band connectivity was widespread in the bvFTD patients compared to HCs. ALS showed a more widespread higher gamma band functional connectivity compared to bvFTD. In conclusion, MEG in early symptomatic ALS patients shows resting-state functional connectivity changes in frontal, limbic and subcortical regions that overlap considerably with bvFTD. The findings show the potential of MEG to detect brain changes in early symptomatic phases of ALS and contribute to our understanding of the disease spectrum, with ALS and bvFTD at the two extreme ends.

Keywords: Amyotrophic lateral sclerosis, Behavioural variant frontotemporal dementia, Functional connectivity, Magnetoencephalography, Oscillatory brain activity, Resting-state

NeuroImage. Clinical (2022), Vol. 34 (35217500) (1 citation)

MEG Oscillatory Slowing in Cognitive Impairment is Associated with the Presence of Subjective Cognitive Decline (2023)

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ABSTRACT The mechanisms behind Alzheimer's disease are not yet fully described, and changes in the electrophysiology of patients across the continuum of the disease could help to understand them. In this work, we study the power spectral distribution of a set of 129 individuals from the Connectomics of Brian Aging and Dementia project.From this sample, we acquired task-free data, with eyes closed, and estimated the power spectral distribution in source space. We compared the spectral profiles of three groups of individuals: 70 healthy controls, 27 patients with amnestic MCI, and 32 individuals showing cognitive impairment without subjective complaints (IWOC).The results showed a slowing of the brain activity in the aMCI patients, when compared to both the healthy controls and the IWOC individuals. These differences appeared both as a decrease in power for high frequency oscillations and an increase in power in alpha oscillations. The slowing of the spectrum was significant mainly in parietal and medial frontal areas.We were able to validate the slowing of the brain activity in individuals with aMCI, appearing in our sample in areas related to the default mode network. However, this pattern did not

appear in the IWOC individuals, suggesting that their condition is not part of the AD continuum. This work raises interesting questions about this group of individuals, and the underlying brain mechanisms behind their cognitive impairment.

Keywords: Cluster-based permutation test, Mild cognitive impairment, Source reconstruction, Spectral power analysis, magnetoencephalography

Clinical EEG and neuroscience (2023), Vol. 54, No. 1 (35188831) (2 citations)

Cognitive Training Modulates Brain Hypersynchrony in a Population at Risk for Alzheimer's Disease (2022)

Suárez-Méndez, Isabel; Bruña, Ricardo; López-Sanz, David; Montejo, Pedro; Montenegro-Peña, Mercedes; Delgado-Losada, María Luisa; Marcos Dolado, Alberto; López-Higes, Ramón; Maestú, Fernando

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BACKGROUND Recent studies demonstrated that brain hypersynchrony is an early sign of dysfunction in Alzheimer's disease (AD) that can represent a proxy for clinical progression. Conversely, non-pharmacological interventions, such as cognitive training (COGTR), are associated with cognitive gains that may be underpinned by a neuroprotective effect on brain synchrony.

OBJECTIVE To study the potential of COGTR to modulate brain synchrony and to eventually revert the hypersynchrony phenomenon that characterizes preclinical AD.

METHODS The effect of COGTR was examined in a sample of healthy controls (HC, n=41, 22 trained) and individuals with subjective cognitive decline (SCD, n=49, 24 trained). Magnetoencephalographic activity and neuropsychological scores were acquired before and after a ten-week COGTR intervention aimed at improving cognitive function and daily living performance. Functional connectivity (FC) was analyzed using the phase-locking value. A mixed-effects ANOVA model with factors time (pre-intervention/post-intervention), training (trained/non-trained), and diagnosis (HC/SCD) was used to investigate significant changes in FC.

RESULTS We found an average increase in alpha-band FC over time, but the effect was different in each group (trained and non-trained). In the trained group (HC and SCD), we report a reduction in the increase in FC within temporo-parietal and temporo-occipital connections. In the trained SCD group, this reduction was stronger and showed a tentative correlation with improved performance in different cognitive tests.

CONCLUSION COGTR interventions could mitigate aberrant increases in FC in preclinical AD, promoting brain synchrony normalization in groups at a higher risk of developing dementia.

Keywords: Cognitive decline, functional neuroimaging, intervention study, longitudinal studies, magnetoencephalography

Journal of Alzheimer's disease: JAD (2022), Vol. 86, No. 3 (35180120) (0 citations)

Spatially resolved neural slowing predicts impairment and amyloid burden in Alzheimer's disease (2022)

Wiesman, Alex I; Murman, Daniel L; Losh, Rebecca A; Schantell, Mikki; Christopher-Hayes, Nicholas J; Johnson, Hallie J; Willett, Madelyn P; Wolfson, Sara L; Losh, Kathryn L; Johnson, Craig M; May, Pamela E; Wilson, Tony W

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ABSTRACT An extensive electrophysiological literature has proposed a pathological 'slowing' of neuronal activity in patients on the Alzheimer's disease spectrum. Supported by numerous studies reporting increases in low-frequency and decreases in high-frequency neural oscillations, this pattern has been suggested as a stable biomarker with potential clinical utility. However, no spatially resolved metric of such slowing exists, stymieing efforts to understand its relation to proteinopathy and clinical outcomes. Further, the assumption that this slowing is occurring in spatially overlapping populations of neurons has not been empirically validated. In the current study, we collected cross-sectional resting state measures of neuronal activity using magnetoencephalography from 38 biomarker-confirmed patients on the Alzheimer's disease spectrum and 20 cognitively normal biomarker-negative older adults. From these data, we compute and validate a new metric of spatially resolved oscillatory deviations from healthy ageing for each patient on the Alzheimer's disease spectrum. Using this Pathological Oscillatory Slowing Index, we show that patients on the Alzheimer's disease spectrum exhibit robust neuronal slowing across a network of temporal, parietal, cerebellar and prefrontal cortices. This slowing effect is shown to be directly relevant to clinical outcomes, as oscillatory slowing in temporal and parietal cortices significantly predicted both general (i.e. Montreal Cognitive Assessment scores) and domain-specific (i.e. attention, language and processing speed) cognitive function. Further, regional amyloid-β accumulation, as measured by quantitative 18F florbetapir PET, robustly predicted the magnitude of this pathological neural slowing effect, and the strength of this relationship between amyloid-β burden and neural slowing also predicted attentional impairments across patients. These findings provide empirical support for a spatially overlapping effect of oscillatory neural slowing in biomarker-confirmed patients on the Alzheimer's disease spectrum, and link this effect to both regional proteinopathy and cognitive outcomes in a spatially resolved manner. The Pathological Oscillatory Slowing Index also represents a novel metric that is of potentially high utility across a number of clinical neuroimaging applications, as oscillatory slowing has also been extensively documented in other patient populations, most notably Parkinson's disease, with divergent spectral and spatial features.

Keywords: magnetoencephalography, mild cognitive impairment, neural oscillations, spontaneous activity

Brain: a journal of neurology (2022), Vol. 145, No. 6 (35088842) (8 citations)

Neuronal synchrony abnormalities associated with subclinical epileptiform activity in early-onset Alzheimer's disease (2022)

Ranasinghe, Kamalini G; Kudo, Kiwamu; Hinkley, Leighton; Beagle, Alexander; Lerner, Hannah; Mizuiri, Danielle; Findlay, Anne; Miller, Bruce L; Kramer, Joel H; Gorno-Tempini, Maria Luisa; Rabinovici, Gil D; Rankin, Katherine P; Garcia, Paul A; Kirsch, Heidi E; Vossel, Keith; Nagarajan, Srikantan S

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ABSTRACT Since the first demonstrations of network hyperexcitability in scientific models of Alzheimer's disease, a growing body of clinical studies have identified subclinical epileptiform activity and associated cognitive decline in patients with Alzheimer's disease. An obvious problem presented in these studies is lack of sensitive measures to detect and quantify network hyperexcitability in human subjects. In this study we examined whether altered neuronal synchrony can be a surrogate marker to quantify network hyperexcitability in patients with Alzheimer's disease. Using

magnetoencephalography (MEG) at rest, we studied 30 Alzheimer's disease patients without subclinical epileptiform activity, 20 Alzheimer's disease patients with subclinical epileptiform activity and 35 age-matched controls. Presence of subclinical epileptiform activity was assessed in patients with Alzheimer's disease by long-term video-EEG and a 1-h resting MEG with simultaneous EEG. Using the resting-state source-space reconstructed MEG signal, in patients and controls we computed the global imaginary coherence in alpha (8-12 Hz) and delta-theta (2-8 Hz) oscillatory frequencies. We found that Alzheimer's disease patients with subclinical epileptiform activity have greater reductions in alpha imaginary coherence and greater enhancements in delta-theta imaginary coherence than Alzheimer's disease patients without subclinical epileptiform activity, and that these changes can distinguish between Alzheimer's disease patients with subclinical epileptiform activity and Alzheimer's disease patients without subclinical epileptiform activity with high accuracy. Finally, a principal component regression analysis showed that the variance of frequency-specific neuronal synchrony predicts longitudinal changes in Mini-Mental State Examination in patients and controls. Our results demonstrate that quantitative neurophysiological measures are sensitive biomarkers of network hyperexcitability and can be used to improve diagnosis and to select appropriate patients for the right therapy in the next-generation clinical trials. The current results provide an integrative framework for investigating network hyperexcitability and network dysfunction together with cognitive and clinical correlates in patients with Alzheimer's disease.

Keywords: epileptiform activity in Alzheimer's disease, imaginary coherence, magnetoencephalography, network hyperexcitability, neuronal synchrony

Brain: a journal of neurology (2022), Vol. 145, No. 2 (34919638) (8 citations)

Generating diagnostic profiles of cognitive decline and dementia using magnetoencephalography (2022)

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ABSTRACT Accurate identification of the underlying cause(s) of cognitive decline and dementia is challenging due to significant symptomatic overlap between subtypes. This study presents a multi-class classification framework for subjects with subjective cognitive decline, mild cognitive impairment, Alzheimer's disease, dementia with Lewy bodies, fronto-temporal dementia and cognitive decline due to psychiatric illness, trained on source-localized resting-state magnetoencephalography data. Diagnostic profiles, describing probability estimates for each of the 6 diagnoses, were assigned to individual subjects. A balanced accuracy rate of 41% and multi-class area under the curve value of 0.75 were obtained for 6-class classification. Classification primarily depended on posterior relative delta, theta and beta power and amplitude-based functional connectivity in the beta and gamma frequency band. Dementia with Lewy bodies (sensitivity: 100%, precision: 20%) and Alzheimer's disease subjects (sensitivity: 51%, precision: 90%) could be classified most accurately. Frontotemporal dementia subjects (sensitivity: 11%, precision: 3%) were most frequently misclassified. Magnetoencephalography biomarkers hold promise to increase diagnostic accuracy in a noninvasive manner. Diagnostic profiles could provide an intuitive tool to clinicians and may facilitate implementation of the classifier in the memory clinic.

Keywords: Cognitive decline, Dementia, Machine learning, Magnetoencephalography, Multi-class classification

Neurobiology of aging (2022), Vol. 111 (34906377) (0 citations)

Analyzing the Effect of Weak External Transcranial Magnetic Stimulation on the Primary Dominant Frequencies of Alzheimer Patients Brain by Using MEG Recordings (2021)

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ABSTRACT Backround and Objectives: Alternative, non-invasive, and non-pharmaceutical options are gaining place in the battle of Alzheimer's Disease treatment control. Lately, the magnetic stimulation of the brain is the most prevalent technique with encouraging results. The aim of this study is to establish any possible change on the Primary Dominant Frequencies (PDF) (range 2-7 Hz) of the affected brain regions in Alzheimer Disease (AD) patients after applying extremely weak Transcranial Magnetic Stimulation. Materials and Methods: For this purpose, all AD patients were scanned with the use of MagnetoEncephaloGraphy (MEG) recordings through a whole-head 122-channel MEG system. Results: Our results exerted statistically significant PDF changes due to weak TMS accompanied by rabid attenuation of clinical symptoms. Conclusion: Thus, this is the first time that a positive therapeutic effect is being demonstrated even at pico-Tesla range magnetic fields in a small clinical group of studies for AD.

Keywords: Alzheimer Disease, magnetoengephalography, pico-Tesla transcranial magnetic stimulation

Medicina (Kaunas, Lithuania) (2021), Vol. 57, No. 11 (34833381) (0 citations)

MEG activity of the dorsolateral prefrontal cortex during optic flow stimulations detects mild cognitive impairment due to Alzheimer's disease (2021)

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ABSTRACT Dorsal stream, which has a neuronal connection with dorsolateral prefrontal cortex (DLPFC), is known to be responsible for detection of motion including optic flow perception. Using magnetoencephalography (MEG), this study aimed to examine neural responses to optic flow stimuli with looming motion in the DLPFC in patients with mild cognitive impairment due to Alzheimer's disease (AD-MCI) compared with cognitively unimpaired participants (CU). We analyzed the neural responses by evaluating maximum source-localized power for the AD-MCI group (n = 11) and CU (n = 20), focusing on six regions of interest (ROIs) that form the DLPFC: right and left dorsal Brodmann area 9/46 (A9/46d), Brodmann area 46 (A46) and ventral Brodmann area 9/46 (A9/46v). We found significant differences in the maximum power between the groups in the left A46 and A9/46v. Moreover, in the left A9/46v, the maximum power significantly correlated with the Wechsler Memory Scale-Revised general memory score and delayed recall score. The maximum power in the left A9/46v also revealed high performance in AD-MCI

versus CU classification with the area under the ROC curve of 0.90. This study demonstrated that MEG during the optic flow task can be useful in discriminating AD-MCI from CU.

PloS one (2021), Vol. 16, No. 11 (34739526) (1 citation)

Sex Differences in Magnetoencephalography-Identified Functional Connectivity in the Human Connectome Project Connectomics of Brain Aging and Dementia Cohort (2022)

Bruña, Ricardo; Maestú, Fernando; López-Sanz, David; Bagic, Anto; Cohen, Ann D; Chang, Yue-Fang; Cheng, Yu; Doman, Jack; Huppert, Ted; Kim, Tae; Roush, Rebecca E; Snitz, Beth E; Becker, James T

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ABSTRACT Introduction: The human brain shows modest traits of sexual dimorphism, with the female brain, on average, 10% smaller than the male brain. These differences do not imply a lowered cognitive performance, but suggest a more optimal brain organization in women. Here we evaluate the patterns of functional connectivity (FC) in women and men from the Connectomics of Brain Aging and Dementia sample. Methods: We used phase locking values to calculate FC from the magnetoencephalography time series in a sample of 138 old adults (87 females and 51 males). We compared the FC patterns between sexes, with the intention of detecting regions with different levels of connectivity. Results: We found a frontal cluster, involving anterior cingulate and the medial frontal lobe, where women showed higher FC values than men. Involved connections included the following: (1) medial parietal areas, such as posterior cingulate cortices and precunei; (2) right insula; and (3) medium cingulate and paracingulate cortices. Moreover, these differences persisted when considering only cognitively intact individuals, but not when considering only cognitively impaired individuals. Discussion: Increased anteroposterior FC has been identified as a biomarker for increased risk of developing cognitive impairment or dementia. In our study, cognitively intact women showed higher levels of FC than their male counterparts. This result suggests that neurodegenerative processes could be taking place in these women, but the changes are undetected by current diagnosis tools. FC, as measured here, might be valuable for early identification of this neurodegeneration.

Keywords: functional connectivity, magnetoencephalography, sex as a biological variable

Brain connectivity (2022), Vol. 12, No. 6 (34726478) (1 citation)

Somatosensory dysfunction is masked by variable cognitive deficits across patients on the Alzheimer's disease spectrum (2021)

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BACKGROUND Alzheimer's disease (AD) is generally thought to spare primary sensory function; however, such interpretations have drawn from a literature that has rarely taken into account the variable cognitive declines seen in patients with AD. As these cognitive domains are now known to modulate cortical somatosensory processing, it remains possible that abnormalities in somatosensory function in patients with AD have been suppressed by neuropsychological variability in previous research.

METHODS In this study, we combine magnetoencephalographic (MEG) brain imaging during a paired-pulse somatosensory gating task with an extensive battery of neuropsychological tests to investigate the influence of cognitive variability on estimated differences in somatosensory function between biomarker-confirmed patients on the AD spectrum and cognitively-normal older adults.

FINDINGS We show that patients on the AD spectrum exhibit largely non-significant differences in somatosensory function when cognitive variability is not considered (p-value range: .020-.842). However, once attention and processing speed abilities are considered, robust differences in gamma-frequency somatosensory response amplitude ($p < .001$) and gating ($p = .004$) emerge, accompanied by significant statistical suppression effects.

INTERPRETATION These findings suggest that patients with AD exhibit insults to functional somatosensory processing in primary sensory cortices, but these effects are masked by variability in cognitive decline across individuals.

FUNDING National Institutes of Health, USA; Fremont Area Alzheimer's Fund, USA.

Keywords: Amyloid-β, Gamma oscillations, Magnetoencephalography, Neuropsychology, Sensory gating

EBioMedicine (2021), Vol. 73 (34689085) (5 citations)

Detection of Mild Cognitive Impairment with MEG Functional Connectivity Using Wavelet-Based Neuromarkers (2021)

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ABSTRACT Studies on developing effective neuromarkers based on magnetoencephalographic (MEG) signals have been drawing increasing attention in the neuroscience community. This study explores the idea of using source-based magnitude-squared spectral coherence as a spatial indicator for effective regions of interest (ROIs) localization, subsequently discriminating the participants with mild cognitive impairment (MCI) from a group of age-matched healthy control (HC) elderly participants. We found that the cortical regions could be divided into two distinctive groups based on their coherence indices. Compared to HC, some ROIs showed increased connectivity (hyper-connected ROIs) for MCI participants, whereas the remaining ROIs demonstrated reduced connectivity (hypo-connected ROIs). Based on these findings, a series of wavelet-based source-level neuromarkers for MCI detection are proposed and explored, with respect to the two distinctive ROI groups. It was found that the neuromarkers extracted from the hyper-connected ROIs performed significantly better for MCI detection than those from the hypo-connected ROIs. The neuromarkers were classified using support vector machine (SVM) and k-NN classifiers and evaluated through Monte Carlo cross-validation. An average recognition rate of 93.83% was obtained using source-reconstructed signals from the hyper-connected ROI group. To better conform to clinical practice settings, a leave-one-out cross-validation (LOOCV) approach was also employed to ensure that the data for testing was from a participant that the clas-

sifier has never seen. Using LOOCV, we found the best average classification accuracy was reduced to 83.80% using the same set of neuromarkers obtained from the ROI group with functional hyper-connections. This performance surpassed the results reported using wavelet-based features by approximately 15%. Overall, our work suggests that (1) certain ROIs are particularly effective for MCI detection, especially when multi-resolution wavelet biomarkers are employed for such diagnosis; (2) there exists a significant performance difference in system evaluation between research-based experimental design and clinically accepted evaluation standards.

Keywords: MCI detection, MEG, connectivity coherence, hyperconnectivity, hypoconnectivity, wavelet-based neuromarker

Sensors (Basel, Switzerland) (2021), Vol. 21, No. 18 (34577423) (1 citation)

Visuospatial alpha and gamma oscillations scale with the severity of cognitive dysfunction in patients on the Alzheimer's disease spectrum (2021)

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BACKGROUND Entrainment of neural oscillations in occipital cortices by external rhythmic visual stimuli has been proposed as a novel therapy for patients with Alzheimer's disease (AD). Despite this increased interest in visual neural oscillations in AD, little is known regarding their role in AD-related cognitive impairment and in particular during visuospatial processing.

METHODS We used source-imaged magnetoencephalography (MEG) and an established visuospatial processing task to elicit multi-spectral neuronal responses in 35 biomarker-confirmed patients on the AD spectrum and 20 biomarker-negative older adults. Neuronal oscillatory responses were imaged to the level of the cortex, and group classifications and neurocognitive relationships were modeled using logistic and linear regression, respectively.

RESULTS Visuospatial neuronal oscillations in the theta, alpha, and gamma ranges significantly predicted the classification of patients on the AD spectrum. Importantly, the direction of these effects differed by response frequency, such that patients on the AD spectrum exhibited weaker alpha-frequency responses in lateral occipital regions, and stronger gamma-frequency responses in the primary visual cortex, as compared to biomarker-negative older adults. In addition, alpha and gamma, but not theta, oscillations robustly predicted cognitive status (i.e., MoCA and MMSE scores), such that patients with neural responses that deviated more from those of healthy older adults exhibited poorer cognitive performance.

CONCLUSIONS We find that the multi-spectral neural dynamics supporting visuospatial processing differentiate patients on the AD spectrum from cognitively normal, biomarker-negative older adults. Oscillations in the alpha and gamma bands also relate to cognitive status in ways that are informative for emerging clinical interventions.

Keywords: Alzheimer’s disease, Magnetoencephalography, Neural oscillations, Source imaging, Visuospatial processing

Alzheimer's research & therapy (2021), Vol. 13, No. 1 (34404472) (7 citations)

Neural dynamics of semantic categorization in semantic variant of primary progressive aphasia (2021)

Borghesani, V; Dale, C L; Lukic, S; Hinkley, Lbn; Lauricella, M; Shwe, W; Mizuiri, D; Honma, S; Miller, Z; Miller, B; Houde, J F; Gorno-Tempini, M L; Nagarajan, S S

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ABSTRACT Semantic representations are processed along a posterior-to-anterior gradient reflecting a shift from perceptual (e.g., it has eight legs) to conceptual (e.g., venomous spiders are rare) information. One critical region is the anterior temporal lobe (ATL): patients with semantic variant primary progressive aphasia (svPPA), a clinical syndrome associated with ATL neurodegeneration, manifest a deep loss of semantic knowledge. We test the hypothesis that svPPA patients perform semantic tasks by over-recruiting areas implicated in perceptual processing. We compared MEG recordings of svPPA patients and healthy controls during a categorization task. While behavioral performance did not differ, svPPA patients showed indications of greater activation over bilateral occipital cortices and superior temporal gyrus, and inconsistent engagement of frontal regions. These findings suggest a pervasive reorganization of brain networks in response to ATL neurodegeneration: the loss of this critical hub leads to a dysregulated (semantic) control system, and defective semantic representations are seemingly compensated via enhanced perceptual processing.

Keywords: anterior temporal lobe, human, magnetoencephalography, neuroscience, primary progressive aphasia, semantic categorization, semantic dementia, semantic variant ppa

eLife (2021), Vol. 10 (34155973) (4 citations)

Reduced synchrony in alpha oscillations during life predicts post mortem neurofibrillary tangle density in early-onset and atypical Alzheimer's disease (2021)

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INTRODUCTION Neurophysiological manifestations selectively associated with amyloid beta and tau depositions in Alzheimer's disease (AD) are useful network biomarkers to identify peptide specific pathological processes. The objective of this study was to validate the associations between reduced neuronal synchrony within alpha oscillations and neurofibrillary tangle (NFT) density in autopsy examination, in patients with AD.

METHODS In a well-characterized clinicopathological cohort of AD patients (n = 13), we quantified neuronal synchrony within alpha (8-12 Hz) and delta-theta (2-8 Hz) oscillations, using magnetoencephalography during the disease course, within six selected neocortical and hippocampal regions, including angular gyrus, superior temporal gurus, middle frontal gyrus, primary motor cortex, CA1, and subiculum, and correlated these with regional NFT density quantified at histopathological examination.

RESULTS Abnormal synchrony in alpha, but not in delta-theta, significantly predicted the NFT density at post mortem neuropathological examination.

DISCUSSION Reduced alpha synchrony is a sensitive neurophysiological index associated with pathological tau, and a potential network biomarker for clinical trials, to gauge the extent of network dysfunction and the degree of rescue in treatments targeting tau pathways in AD.

Keywords: Alzheimer's disease, alpha oscillations, magnetoencephalography, neurofibrillary tangle density, neuropathology, neurophysiology

Alzheimer's & dementia: the journal of the Alzheimer's Association (2021), Vol. 17, No. 12 (33884753) (7 citations)

Hypersynchronized Magnetoencephalography Brain Networks in Patients with Mild Cognitive Impairment and Alzheimer's Disease in Down Syndrome (2021)

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ABSTRACT Introduction: The majority of individuals with Down syndrome (DS) show signs of Alzheimer's disease (AD) neuropathology in their fourth decade. However, there is a lack of specific markers for characterizing the disease stages while considering this population's differential features. Methods: Forty-one DS individuals participated in the study, and were classified into three groups according to their clinical status: Alzheimer's disease (AD-DS), mild cognitive impairment (MCI-DS), and controls (CN-DS). We performed an exhaustive neuropsychological evaluation and assessed brain functional connectivity (FC) from magnetoencephalographic recordings. Results: Compared with CN-DS, both MCI-DS and AD-DS showed a pattern of increased FC within the high alpha band. The neuropsychological assessment showed a generalized cognitive impairment, especially affecting mnestic functions, in MCI-DS and, more pronouncedly, in AD-DS. Discussion: These findings might help to characterize the AD-continuum in DS. In addition, they support the role of the excitatory/inhibitory imbalance as a key pathophysiological factor in AD. Impact statement The pattern of functional connectivity (FC) hypersynchronization found in this study resembles the largely reported Alzheimer's disease (AD) FC evolution pattern in population with typical development. This study supports the hypothesis of the excitatory/inhibitory imbalance as a key pathophysiological factor in AD, and its conclusions could help in the characterization and prediction of Down syndrome individuals with a greater likelihood of converting to dementia.

Keywords: Alzheimer's disease, Down syndrome, functional connectivity, hypersynchronization, magnetoencephalography, mild cognitive impairment

Brain connectivity (2021), Vol. 11, No. 9 (33858203) (5 citations)

Altered mismatch response precedes gray matter atrophy in subjective cognitive decline (2021)

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ABSTRACT The cross-sectional identification of subjective cognitive decline (SCD) in cognitively normal adults is particularly important for the early effective prevention or intervention of the future development of mild cognitive impairments (MCI) or Alzheimer's disease (AD). A pre-attentive neurophysiological signal that reflects the brain's ability to detect the changes of the environment is called mismatch negativity (MMN) or its magnetic counterpart (MMNm). It has been shown that patients with MCI or AD demonstrate reduced MMN/MMNm responses, while the exact profile of MMN/MMNm in SCD is substantially unknown. We applied magnetoencephalographic recordings to interrogate MMNm activities in healthy controls (HC, n = 29) and individuals with SCD (n = 26). Furthermore, we analyzed gray matter (GM) volumes in the MMNm-related regions through voxel-based morphometry and performed apolipoprotein E4 (APOE4) genotyping for all the participants. Our results showed that there were no significant differences in GM volume and proportions of APOE4 carriers between HC and SCD groups. However, individuals with SCD exhibited weakened z-corrected MMNm responses in the left inferior parietal lobule and right inferior frontal gyrus (IFG) as compared to HC. Based on the regions showing significant between-group differences, z-corrected MMNm amplitudes of the right IFG significantly correlated with the memory performance among the SCD participants. Our data suggest that neurophysiological changes of the brain, as indexed by MMNm, precede structural atrophy in the individuals with SCD compared to those without SCD.

Keywords: APOE4, MEG, MRI, mismatch negativity, subjective memory complaint

Psychophysiology (2021), Vol. 58, No. 6 (33792049) (3 citations)

Neuromagnetic evidence of abnormal automatic inhibitory function in subjective memory complaint (2021)

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ABSTRACT Subjective memory complaint (SMC), a self-perceived worsening in memory capacity concurrent with normal performance on standardized cognitive assessments, is considered a risk factor for the development of Alzheimer's disease (AD). Deficient sensory gating (SG), referring to the lack of automatic inhibition of neural responses to the second identical stimulus, has been documented in prodromal and incident AD patients. However, it remains unknown whether the cognitively normal elderly with SMC demonstrate alterations of SG function compared with those without SMC. A total of 19 healthy controls (HC) and 16 SMC subjects were included in the present study. Neural responses to the auditory paired-stimulus paradigm were recorded by the magnetoencephalography and analyzed by the distributed source imaging method of minimum norm estimate. The SG of M50 and M100 components were measured using the amplitude ratio of the second response over the first response at the cortical level. Compared to HC, subjects with SMC showed significantly increased M50 SG ratios in the inferior parietal lobule (IPL). Furthermore, M50 SG ratios in the right IPL yielded an acceptable discriminative

ability to distinguish SMC from HC. However, we did not find a significant association between SG ratios and cognitive function requiring inhibitory control either in the HC or SMC group. In conclusion, although SMC subjects have intact cognitive functioning revealed by objective neuropsychological tests, their deficits in automatic inhibitory function could be detected through neurophysiological recordings. Our results suggest that altered brain function occurs in SMC prior to the obvious decline of cognitive performance.

Keywords: Alzheimer's disease, inferior parietal lobule, magnetoencephalography, sensory gating, subjective cognitive decline, subjective memory complaint

The European journal of neuroscience (2021), Vol. 53, No. 10 (33754412) (3 citations)

GABAergic cortical network physiology in frontotemporal lobar degeneration (2021)

Adams, Natalie E; Hughes, Laura E; Rouse, Matthew A; Phillips, Holly N; Shaw, Alexander D; Murley, Alexander G; Cope, Thomas E; Bevan-Jones, W Richard; Passamonti, Luca; Street, Duncan; Holland, Negin; Nesbitt, David; Friston, Karl; Rowe, James B

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ABSTRACT The clinical syndromes caused by frontotemporal lobar degeneration are heterogeneous, including the behavioural variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy. Although pathologically distinct, they share many behavioural, cognitive and physiological features, which may in part arise from common deficits of major neurotransmitters such as γ-aminobutyric acid (GABA). Here, we quantify the GABAergic impairment and its restoration with dynamic causal modelling of a double-blind placebo-controlled crossover pharmacomagnetoencephalography study. We analysed 17 patients with bvFTD, 15 patients with progressive supranuclear palsy, and 20 healthy age- and gender-matched controls. In addition to neuropsychological assessment and structural MRI, participants undertook two magnetoencephalography sessions using a roving auditory oddball paradigm: once on placebo and once on 10 mg of the oral GABA reuptake inhibitor tiagabine. A subgroup underwent ultrahigh-field magnetic resonance spectroscopy measurement of GABA concentration, which was reduced among patients. We identified deficits in frontotemporal processing using conductance-based biophysical models of local and global neuronal networks. The clinical relevance of this physiological deficit is indicated by the correlation between top-down connectivity from frontal to temporal cortex and clinical measures of cognitive and behavioural change. A critical validation of the biophysical modelling approach was evidence from parametric empirical Bayes analysis that GABA levels in patients, measured by spectroscopy, were related to posterior estimates of patients' GABAergic synaptic connectivity. Further evidence for the role of GABA in frontotemporal lobar degeneration came from confirmation that the effects of tiagabine on local circuits depended not only on participant group, but also on individual baseline GABA levels. Specifically, the phasic inhibition of deep cortico-cortical pyramidal neurons following tiagabine, but not placebo, was a function of GABA concentration. The study provides proof-of-concept for the potential of dynamic causal modelling to elucidate mechanisms of human neurodegenerative disease, and explains the variation in response to candidate therapies among patients. The laminar- and neurotransmitter-specific features of the modelling framework, can be used to study other treatment approaches and disorders. In the context of frontotemporal lobar degeneration, we suggest that neurophysiological restoration in selected patients, by targeting neurotransmitter deficits, could be used to bridge between clinical and preclinical models of disease, and inform the personalized selection of drugs and stratification of patients for future clinical trials.

Keywords: GABA, conductance-based modelling, dynamic causal modelling, frontotemporal dementia, progressive supranuclear palsy

Brain: a journal of neurology (2021), Vol. 144, No. 7 (33710299) (10 citations)

Advances in neuroimaging to support translational medicine in dementia (2021)

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ABSTRACT Advances in neuroimaging are ideally placed to facilitate the translation from progress made in cellular genetics and molecular biology of neurodegeneration into improved diagnosis, prevention and treatment of dementia. New positron emission tomography (PET) ligands allow one to quantify neuropathology, inflammation and metabolism in vivo safely and reliably, to examine mechanisms of human disease and support clinical trials. Developments in MRI-based imaging and neurophysiology provide complementary quantitative assays of brain function and connectivity, for the direct testing of hypotheses of human pathophysiology. Advances in MRI are also improving the quantitative imaging of vascular risk and comorbidities. In combination with large datasets, open data and artificial intelligence analysis methods, new informatics-based approaches are set to enable accurate single-subject inferences for diagnosis, prediction and treatment that have the potential to deliver precision medicine for dementia. Here, we show, through the use of critically appraised worked examples, how neuroimaging can bridge the gaps between molecular biology, neural circuits and the dynamics of the core systems that underpin complex behaviours. We look beyond traditional structural imaging used routinely in clinical care, to include ultrahigh field MRI (7T MRI), magnetoencephalography and PET with novel ligands. We illustrate their potential as safe, robust and sufficiently scalable to be viable for experimental medicine studies and clinical trials. They are especially informative when combined in multimodal studies, with model-based analyses to test precisely defined hypotheses.

Keywords: MRI, PET, dementia, functional imaging, image analysis

Journal of neurology, neurosurgery, and psychiatry (2021), Vol. 92, No. 3 (33568448) (4 citations)

In vivo tau pathology is associated with synaptic loss and altered synaptic function (2021)

Coomans, Emma M; Schoonhoven, Deborah N; Tuncel, Hayel; Verfaillie, Sander C J; Wolters, Emma E; Boellaard, Ronald; Ossenkoppele, Rik; den Braber, Anouk; Scheper, Wiep; Schober, Patrick; Sweeney, Steven P; Ryan, J Michael; Schuit, Robert C; Windhorst, Albert D; Barkhof, Frederik; Scheltens, Philip; Golla, Sandeep S V; Hillebrand, Arjan; Gouw, Alida A; van Berckel, Bart N M

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BACKGROUND The mechanism of synaptic loss in Alzheimer's disease is poorly understood and may be associated with tau pathology. In this combined positron emission tomography (PET) and magnetoencephalography (MEG) study, we aimed to investigate spatial associations between regional tau pathology ([[18] F]flortaucipir PET), synaptic density (synaptic vesicle 2A [[11]C]UCB-J PET) and synaptic function (MEG) in Alzheimer's disease.

METHODS Seven amyloid-positive Alzheimer's disease subjects from the Amsterdam Dementia Cohort underwent dynamic 130-min [[18]F]flortaucipir PET, dynamic 60-min [[11]C]UCB-J PET with arterial sampling and 2 × 5-min resting-state MEG measurement. [[18]F] flortaucipir- and [[11]C]UCB-J-specific binding (binding potential, BPND) and MEG spectral measures (relative delta, theta and alpha power; broadband power; and peak frequency) were assessed in cortical brain regions of interest. Associations between regional [[18]F] flortaucipir BPND, [[11]C]UCB-J BPND and MEG spectral measures were assessed using Spearman correlations and generalized estimating equation models.

RESULTS Across subjects, higher regional [[18]F]flortaucipir uptake was associated with lower [[11]C]UCB-J uptake. Within subjects, the association between [[11] C]UCB-J and [[18]F]flortaucipir depended on within-subject neocortical tau load; negative associations were observed when neocortical tau load was high, gradually changing into opposite patterns with decreasing neocortical tau burden. Both higher [[18]F]flortaucipir and lower [[11]C]UCB-J uptake were associated with altered synaptic function, indicative of slowing of oscillatory activity, most pronounced in the occipital lobe.

CONCLUSIONS These results indicate that in Alzheimer's disease, tau pathology is closely associated with reduced synaptic density and synaptic dysfunction.

Keywords: Alzheimer, MEG, PET, Synaptic density, Synaptic function, Tau

Alzheimer's research & therapy (2021), Vol. 13, No. 1 (33546722) (24 citations)

Cortical connectivity of the nucleus basalis of Meynert in Parkinson's disease and Lewy body dementias (2021)

Oswal, Ashwini; Gratwicke, James; Akram, Harith; Jahanshahi, Marjan; Zaborszky, Laszlo; Brown, Peter; Hariz, Marwan; Zrinzo, Ludvic; Foltynie, Tom; Litvak, Vladimir

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ABSTRACT Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are related conditions that are associated with cholinergic system dysfunction. Dysfunction of the nucleus basalis of Meynert (NBM), a basal forebrain structure that provides the dominant source of cortical cholinergic innervation, has been implicated in the pathogenesis of both PDD and DLB. Here we leverage the temporal resolution of magnetoencephalography with the spatial resolution of MRI tractography to explore the intersection of functional and structural connectivity of the NBM in a unique cohort of PDD and DLB patients undergoing deep brain stimulation of this structure. We observe that NBM-cortical structural and functional connectivity correlate within spatially and spectrally segregated networks including: (i) a beta band network to supplementary motor area, where activity in this region was found to drive activity in the NBM; (ii) a delta/theta band network to medial temporal lobe structures encompassing the parahippocampal gyrus; and (iii) a delta/theta band network to visual areas including lingual gyrus. These findings reveal functional networks of the NBM that are likely to subserve important roles in motor control, memory and visual function, respectively. Furthermore, they motivate future studies aimed at disentangling network contribution to disease phenotype.

Keywords: DBS, DTI, MEG, coherence, oscillations

Brain: a journal of neurology (2021), Vol. 144, No. 3 (33521808) (14 citations)

Alterations in resting-state network dynamics along the Alzheimer's disease continuum (2020)

Puttaert, D; Coquelet, N; Wens, V; Peigneux, P; Fery, P; Rovai, A; Trotta, N; Sadeghi, N; Coolen, T; Bier, J-C; Goldman, S; De Tiège, X

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ABSTRACT Human brain activity is intrinsically organized into resting-state networks (RSNs) that transiently activate or deactivate at the sub-second timescale. Few neuroimaging studies have addressed how Alzheimer's disease (AD) affects these fast temporal brain dynamics, and how they relate to the cognitive, structural and metabolic abnormalities characterizing AD. We aimed at closing this gap by investigating both brain structure and function using magnetoencephalography (MEG) and hybrid positron emission tomography-magnetic resonance (PET/MR) in 10 healthy elders, 10 patients with subjective cognitive decline (SCD), 10 patients with amnestic mild cognitive impairment (aMCI) and 10 patients with typical Alzheimer's disease with dementia (AD). The fast activation/deactivation state dynamics of RSNs were assessed using hidden Markov modeling (HMM) of power envelope fluctuations at rest measured with MEG. Correlations were sought between temporal properties of HMM states and participants' cognitive test scores, whole hippocampal grey matter volume and regional brain glucose metabolism. The posterior default-mode network (DMN) was less often activated and for shorter durations in AD patients than matched healthy elders. No significant difference was found in patients with SCD or aMCI. The time spent by participants in the activated posterior DMN state did not correlate significantly with cognitive scores, nor with the whole hippocampal volume. However, it correlated positively with the regional glucose consumption in the right dorsolateral prefrontal cortex (DLPFC). AD patients present alterations of posterior DMN power activation dynamics at rest that identify an additional electrophysiological correlate of AD-related synaptic and neural dysfunction. The right DLPFC may play a causal role in the activation of the posterior DMN, possibly linked to the occurrence of mind wandering episodes. As such, these data might suggest a neural correlate of the decrease in mind wandering episodes reported in pathological aging.

Scientific reports (2020), Vol. 10, No. 1 (33319785) (14 citations)

Predicting the outcome of non-pharmacological treatment for patients with dementia-related mild cognitive impairment (2020)

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ABSTRACT Dementia is a progressive cognitive syndrome, with few effective pharmacological treatments that can slow its progress. Hence, non-pharmacological treatments (NPTs) play an important role in improving patient symptoms and quality of life. Designing the optimal personalised NPT strategy relies on objectively and quantitatively predicting the treatment outcome. Magnetoencephalography (MEG) findings can reflect the cognitive status of patients with dementia, and thus potentially predict NPT outcome. In the present study, 16 participants with cognitive impairment underwent NPT for several months. Their cognitive performance was evaluated based on the Mini-Mental State Examination and the Alzheimer's Disease Assessment Scale - Cognitive at the beginning and end of the NPT period, while resting-state brain activity was evaluated using MEG during the NPT period. Our results showed that the spectral properties of MEG signals predicted the changes in cognitive performance scores. High frequency oscillatory intensity at the right superior frontal gyrus medial segment, opercular part of the inferior frontal gyrus, triangular part of the inferior frontal gyrus, post central gyrus, and angular gyrus predicted the changes in cognitive performance scores. Thus, resting-state brain activity may be a powerful tool in designing personalised NPT.

Keywords: dementia, mild cognitive impairment, non-pharmacological treatment, power spectrum, spectral parameters

Aging (2020), Vol. 12, No. 23 (33289701) (6 citations)

Functional Connectivity Hypersynchronization in Relatives of Alzheimer's Disease Patients: An Early E/I Balance Dysfunction? (2021)

Ramírez-Toraño, F; Bruña, R; de Frutos-Lucas, J; Rodríguez-Rojo, I C; Marcos de Pedro, S; Delgado-Losada, M L; Gómez-Ruiz, N; Barabash, A; Marcos, A; López Higes, R; Maestú, F

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ABSTRACT Alzheimer's disease (AD) studies on animal models, and humans showed a tendency of the brain tissue to become hyperexcitable and hypersynchronized, causing neurodegeneration. However, we know little about either the onset of this phenomenon or its early effects on functional brain networks. We studied functional connectivity (FC) on 127 participants (92 middle-age relatives of AD patients and 35 age-matched nonrelatives) using magnetoencephalography. FC was estimated in the alpha band in areas known both for early amyloid accumulation and disrupted FC in MCI converters to AD. We found a frontoparietal network (anterior cingulate cortex, dorsal frontal, and precuneus) where relatives of AD patients showed hypersynchronization in high alpha (not modulated by APOE-ε4 genotype) in comparison to age-matched nonrelatives. These results represent the first evidence of neurophysiological events causing early network disruption in humans, opening a new perspective for intervention on the excitation/inhibition unbalance.

Keywords: early detection, excitation/inhibition unbalance, magnetoencephalography, network disruption, relatives of Alzheimer's disease patients

Cerebral cortex (New York, N.Y.: 1991) (2021), Vol. 31, No. 2 (33108468) (9 citations)

Predicting the progression of mild cognitive impairment using machine learning: A systematic, quantitative and critical review (2021)

Ansart, Manon; Epelbaum, Stéphane; Bassignana, Giulia; Bône, Alexandre; Bottani, Simona; Cattai, Tiziana; Couronné, Raphaël; Faouzi, Johann; Koval, Igor; Louis, Maxime; Thibeau-Sutre, Elina; Wen, Junhao; Wild, Adam; Burgos, Ninon; Dormont, Didier; Colliot, Olivier; Durrleman, Stanley

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ABSTRACT We performed a systematic review of studies focusing on the automatic prediction of the progression of mild cognitive impairment to Alzheimer's disease (AD) dementia, and a quantitative analysis of the methodological choices impacting performance. This review included 172 articles, from which 234 experiments were extracted. For each of them, we reported the used data set, the feature types, the algorithm type, performance and potential methodological issues. The impact of these characteristics on the performance was evaluated using a multivariate mixed effect linear regressions. We found that using cognitive, fluorodeoxyglucose-positron emission tomography or potentially electroencephalography and magnetoencephalography variables significantly improved predictive performance compared to not including them, whereas including other modalities, in particular T1 magnetic resonance imaging, did not show a significant effect. The good performance of cognitive assessments questions the wide use of imaging for predicting the progression to AD and advocates for exploring further fine domain-specific cognitive assessments. We also identified several methodological issues, including the absence of a test set, or its use for feature selection or parameter tuning in nearly a fourth of the papers. Other issues, found in 15% of the studies, cast doubts on the relevance of the method to clinical practice. We also highlight that short-term predictions are likely not to be better than predicting that subjects stay stable over time. These issues highlight the importance of adhering to good practices for the use of machine learning as a decision support system for the clinical practice.

Keywords: Alzheimer’s disease, Automatic prediction, Cognition, Mild cognitive impairment, Progression, Quantitative review

Medical image analysis (2021), Vol. 67 (33091740) (20 citations)

Functional decline of the precuneus associated with mild cognitive impairment: Magnetoencephalographic observations (2020)

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ABSTRACT Mild Cognitive Impairment (MCI) is a border or precursor state of dementia. To optimize implemented interventions for MCI, it is essential to clarify the underlying neural mechanisms. However, knowledge regarding the brain regions responsible for MCI is still limited. Here, we implemented the Montreal Cognitive Assessment (MoCA) test, a screening tool for MCI, in 20 healthy elderly participants (mean age, 67.5 years), and then recorded magnetoencephalograms (MEG) while they performed a visual sequential memory task. In the task, each participant memorized the four possible directions of seven sequentially presented arrow images. Recall accuracy for beginning items of the memory sequence was significantly positively related with MoCA score. Meanwhile, MEG revealed stronger alpha-band (8-13 Hz) rhythm desynchronization bilaterally in the precuneus (PCu) for higher MoCA (normal) participants. Most importantly, this PCu desynchronization response weakened in correspondence with lower MoCA score during the beginning of sequential memory encoding, a time period that should rely on working memory and be affected by declined cognitive function. Our results suggest that deactivation of the PCu is associated with early MCI, and corroborate pathophysiological findings based on post-mortem tissue which have implicated hypoperfusion of the PCu in early stages of Alzheimer disease. Our results indicate the possibility that cognitive decline can be detected early and non-invasively by monitoring PCu activity with electrophysiological methods.

PloS one (2020), Vol. 15, No. 9 (32986743) (6 citations)

Age and APOE genotype affect the relationship between objectively measured physical activity and power in the alpha band, a marker of brain disease (2020)

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BACKGROUND Electrophysiological studies show that reductions in power within the alpha band are associated with the Alzheimer's disease (AD) continuum. Physical activity (PA) is a protective factor that has proved to reduce AD risk and pathological brain burden. Previous research has confirmed that exercise increases power in the alpha range. However, little is known regarding whether other non-modifiable risk factors for AD, such as increased age or APOE ε4 carriage, alter the association between PA and power in the alpha band.

METHODS The relationship between PA and alpha band power was examined in a sample of 113 healthy adults using magnetoencephalography. Additionally, we explored whether ε4 carriage and age modulate this association. The correlations between alpha power and gray matter volumes and cognition were also investigated.

RESULTS We detected a parieto-occipital cluster in which PA positively correlated with alpha power. The association between PA and alpha power remained following stratification of the cohort by genotype. Younger and older adults were investigated separately, and only younger adults exhibited a positive relationship between PA and alpha power. Interestingly, when four groups were created based on age (younger-older adult) and APOE (E3/E3-E3/E4), only younger E3/E3 (least predicted risk) and older E3/E4 (greatest predicted risk) had associations between greater alpha power and higher PA. Among older E3/E4, greater alpha power in these regions was associated with improved memory and preserved brain structure.

CONCLUSION PA could protect against the slowing of brain activity that characterizes the AD continuum, where it is of benefit for all individuals, especially E3/E4 older adults.

Keywords: APOE ε4, Alpha power, Alzheimer’s disease, Magnetoencephalography, Physical activity

Alzheimer's research & therapy (2020), Vol. 12, No. 1 (32962736) (6 citations)

Detection of early stages of Alzheimer's disease based on MEG activity with a randomized convolutional neural network (2020)

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ABSTRACT The early detection of Alzheimer's disease can potentially make eventual treatments more effective. This work presents a deep learning model to detect early symptoms of Alzheimer's disease using synchronization measures obtained with magnetoencephalography. The proposed model is a novel deep learning architecture based on an ensemble of randomized blocks formed by a sequence of 2D-convolutional, batch-normalization and pooling layers. An important challenge is to avoid overfitting, as the number of features is very high (25755) compared to the number of samples (132 patients). To address this issue the model uses an ensemble of identical sub-models all sharing weights, with a final stage that performs an average across sub-models. To facilitate the exploration of the feature space, each sub-model receives a random permutation of features. The features correspond to magnetic signals reflecting neural activity and are arranged in a matrix structure interpreted as a 2D image that is processed by 2D convolutional networks. The proposed detection model is a binary classifier (disease/non-disease), which compared to other deep learning architectures and classic machine learning classifiers, such as random forest and support vector machine, obtains the best classification performance results with an average F1-score of 0.92. To perform the comparison a strict validation procedure is proposed, and a thorough study of results is provided.

Keywords: Alzheimer’s disease detection, Convolutional neural network, Deep learning, Ensemble model, Magnetoencephalography

Artificial intelligence in medicine (2020), Vol. 107 (32828459) (15 citations)

Taking the sublexical route: brain dynamics of reading in the semantic variant of primary progressive aphasia (2020)

Borghesani, Valentina; Hinkley, Leighton B N; Ranasinghe, Kamalini G; Thompson, Megan M C; Shwe, Wendy; Mizuiri, Danielle; Lauricella, Michael; Europa, Eduardo; Honma, Susanna; Miller, Zachary; Miller, Bruce; Vossel, Keith; Henry, Maya M L; Houde, John F; Gorno-Tempini, Maria L; Nagarajan, Srikantan S

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ABSTRACT Reading aloud requires mapping an orthographic form to a phonological one. The mapping process relies on sublexical statistical regularities (e.g. 'oo' to |u |) or on learned lexical associations between a specific visual form and a series of sounds (e.g. yacht to/j t/). Computational, neuroimaging, and neuropsychological evidence suggest that sublexical, phonological and lexico-semantic processes rely on partially distinct neural substrates: a dorsal (occipito-parietal) and a ventral (occipito-temporal) route, respectively. Here, we investigated the spatiotemporal features of orthography-to-phonology mapping, capitalizing on the time resolution of magnetoencephalography and the unique clinical model offered by patients with semantic variant of primary progressive aphasia (svPPA). Behaviourally, patients with svPPA manifest marked lexico-semantic impairments including difficulties in reading words with exceptional orthographic to phonological correspondence (irregular words). Moreover, they present with focal neurodegeneration in the anterior temporal lobe, affecting primarily the ventral, occipito-temporal, lexical route. Therefore, this clinical population allows for testing of specific hypotheses on the neural implementation of the dual-route model for reading, such as whether damage to one route can be compensated by over-reliance on the other. To this end, we reconstructed and analysed time-resolved whole-brain activity in 12 svPPA patients and 12 healthy age-matched control subjects while reading irregular words (e.g. yacht) and pseudowords (e.g. pook). Consistent with previous findings that the dorsal route is involved in sublexical, phonological processes, in control participants we observed enhanced neural activity over dorsal occipito-parietal cortices for pseudowords, when compared to irregular words. This activation was manifested in the beta-band (12-30 Hz), ramping up slowly over 500 ms after stimulus onset and peaking at 800 ms, around response selection and production. Consistent with our prediction, svPPA patients did not exhibit this temporal pattern of neural activity observed in controls this contrast. Furthermore, a direct comparison of neural activity between patients and controls revealed a dorsal spatiotemporal cluster during irregular word reading. These findings suggest that the sublexical/phonological route is involved in processing both irregular and pseudowords in svPPA. Together these results provide further evidence supporting a dual-route model for reading aloud mediated by the interplay between lexico-semantic and sublexical/phonological neurocognitive systems. When the ventral route is damaged, as in the case of neurodegeneration affecting the anterior temporal lobe, partial compensation appears to be possible by over-recruitment of the slower, serial attention-dependent, dorsal one.

Keywords: MEG, dual-model of reading, semantic variant primary progressive aphasia, surface dyslexia

Brain: a journal of neurology (2020), Vol. 143, No. 8 (32789455) (11 citations)

Resting state activity and connectivity of the nucleus basalis of Meynert and globus pallidus in Lewy body dementia and Parkinson's disease dementia (2020)

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ABSTRACT Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are two related diseases which can be difficult to distinguish. There is no objective biomarker which can reliably differentiate between them. The synergistic combination of electrophysiological and neuroimaging approaches is a powerful method for interrogation of functional brain networks in vivo. We recorded bilateral local field potentials (LFPs) from the nucleus basalis of Meynert (NBM) and the internal globus pallidus (GPi) with simultaneous cortical magnetoencephalography (MEG) in six PDD and five DLB patients undergoing surgery for deep brain stimulation (DBS) to look for differences in underlying resting-state network pathophysiology. In both patient groups we observed spectral peaks in the theta (2-8 Hz) band in both the NBM and the GPi. Furthermore, both the NBM and the GPi exhibited similar spatial and spectral patterns of coupling with the cortex in the two disease states. Specifically, we report two distinct coherent networks between the NBM/GPi and cortical regions: (1) a theta band (2-8 Hz) network linking the NBM/GPi to temporal cortical regions, and (2) a beta band (13-22 Hz) network coupling the NBM/GPi to sensorimotor areas. We also found differences between the two disease groups: oscillatory power in the low beta (13-22Hz) band was significantly higher in the globus pallidus in PDD patients compared to DLB, and coherence in the high beta (22-35Hz) band between the globus pallidus and lateral sensorimotor cortex was significantly higher in DLB patients compared to PDD. Overall, our findings reveal coherent networks of the NBM/GPi region that are common to both DLB and PDD. Although the neurophysiological differences between the two conditions in this study are confounded by systematic differences in DBS lead trajectories and motor symptom severity, they lend support to the hypothesis that DLB and PDD, though closely related, are distinguishable from a neurophysiological perspective.

Keywords: Basal forebrain, Basal ganglia, Human, Network, Pallidum

NeuroImage (2020), Vol. 221 (32711059) (10 citations)

Spontaneous MEG activity of the cerebral cortex during eyes closed and open discriminates Alzheimer's disease from cognitively normal older adults (2020)

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ABSTRACT This study aimed to examine whether magnetoencephalography (MEG) is useful to detect early stage Alzheimer's disease (AD). We analyzed MEG data from the early stage AD group (n = 20; 6 with mild cognitive impairment due to AD and 14 with AD dementia) and cognitively normal control group (NC, n = 27). MEG was recorded during resting eyes closed (EC) and eyes open (EO), and the following 6 values for each of 5 bands (θ1: 4-6, θ2: 6-8, α1: 8-10, α2: 10-13, β: 13-20 Hz) in the cerebral 68 regions were compared between the groups: (1) absolute power during EC and (2) EO, (3) whole cerebral normalization (WCN) power during EC and (4) EO, (5) difference of the absolute powers between the EC and EO conditions (the EC-EO difference), and (6) WCN value of the EC-EO difference. We found significant differences between the groups in the WCN powers during the EO condition, and the EC-EO differences. Using a Support Vector Machine classifier, a discrimination accuracy of 83% was obtained and an AUC in an ROC analysis was 0.91. This study demonstrates that MEG during resting EC and EO is useful in discriminating between early stage AD and NC.

Scientific reports (2020), Vol. 10, No. 1 (32499487) (3 citations)

Role of Magnetoencephalography in the Early Stages of Alzheimer Disease (2020)

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ABSTRACT As synaptic dysfunction is an early manifestation of Alzheimer disease (AD) pathology, magnetoencephalography (MEG) is capable of detecting disruptions by assessing the synchronized oscillatory activity of thousands of neurons that rely on the integrity of neural connections. MEG findings include slowness of the oscillatory activity, accompanied by a reduction of the alpha band power, and dysfunction of the functional networks. These findings are associated with the neuropathology of the disease and cognitive impairment. These neurophysiological biomarkers predict which patients with mild cognitive impairment will develop dementia. MEG has demonstrated its utility as a noninvasive biomarker for early detection of AD.

Keywords: Alzheimer disease, Functional connectivity, Magnetoencephalography, Mild cognitive impairment, Power, Preclinical stages, Prodromal stages

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336408) (3 citations)

The relationship between physical activity, apolipoprotein E ε4 carriage, and brain health (2020)

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BACKGROUND Neuronal hyperexcitability and hypersynchrony have been described as key features of neurophysiological dysfunctions in the Alzheimer's disease (AD) continuum. Conversely, physical activity (PA) has been associated with improved brain health and reduced AD risk. However, there is controversy regarding whether AD genetic risk (in terms of APOE ε4 carriage) modulates these relationships. The utilization of multiple outcome measures within one sample may strengthen our understanding of this complex phenomenon.

METHOD The relationship between PA and functional connectivity (FC) was examined in a sample of 107 healthy older adults using magnetoencephalography. Additionally, we explored whether ε4 carriage modulates this association. The correlation between FC and brain structural integrity, cognition, and mood was also investigated.

RESULTS A relationship between higher PA and decreased FC (hyposynchrony) in the left temporal lobe was observed among all individuals (across the whole sample, in ε4 carriers, and in ε4 non-carriers), but its effects manifest differently according to genetic risk. In ε4 carriers, we report an association between this region-specific FC profile and preserved brain structure (greater gray matter volumes and higher integrity of white matter tracts). In this group, decreased FC also correlated with reduced anxiety levels. In ε4 non-carriers, this profile is associated with improved cognition (working and episodic memory).

CONCLUSIONS PA could mitigate the increase in FC (hypersynchronization) that characterizes preclinical AD, being beneficial for all individuals, especially ε4 carriers.

Keywords: APOE, Alzheimer's disease, MEG, Physical activity, Synaptic function, Temporal lobe

Alzheimer's research & therapy (2020), Vol. 12, No. 1 (32331531) (15 citations)

Non-pharmacological treatment changes brain activity in patients with dementia (2020)

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ABSTRACT Non-pharmacological treatment (NPT) improves cognitive functions and behavioural disturbances in patients with dementia, but the underlying neural mechanisms are unclear. In this observational study, 21 patients with dementia received NPTs for several months. Patients were scanned using magnetoencephalography twice during the NPT period to evaluate NPT effects on resting-state brain activity. Additionally, cognitive functions and behavioural disturbances were measured using the Mini-Mental State Examination (MMSE-J) and a short version of the Dementia Behaviour Disturbance Scale (DBD-13) at the beginning and the end of the NPT period. In contrast to the average DBD-13 score, the average MMSE-J score improved after the NPT period. Magnetoencephalography data revealed a reduced alpha activity in the right temporal lobe and fusiform gyrus, as well as an increased low-gamma activity in the right angular gyrus. DBD-13

score changes were correlated with beta activity in the sensorimotor area. These findings corroborate previous studies confirming NPT effects on brain activity in healthy participants and people at risk of dementia. Our results provide additional evidence that brains of patients with dementia have the capacity for plasticity, which may be responsible for the observed NPT effects. In dementia, NPT might lead to improvements in the quality of life.

Scientific reports (2020), Vol. 10, No. 1 (32317774) (16 citations)

Tau pathology in early Alzheimer's disease is linked to selective disruptions in neurophysiological network dynamics (2020)

Kocagoncu, Ece; Quinn, Andrew; Firouzian, Azadeh; Cooper, Elisa; Greve, Andrea; Gunn, Roger; Green, Gary; Woolrich, Mark W; Henson, Richard N; Lovestone, Simon; Deep and Frequent Phenotyping study team; Rowe, James B

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ABSTRACT Understanding the role of Tau protein aggregation in the pathogenesis of Alzheimer's disease is critical for the development of new Tau-based therapeutic strategies to slow or prevent dementia. We tested the hypothesis that Tau pathology is associated with functional organization of widespread neurophysiological networks. We used electro-magnetoencephalography with [[18]F]AV-1451 PET scanning to quantify Tau-dependent network changes. Using a graph theoretical approach to brain connectivity, we quantified nodal measures of functional segregation, centrality, and the efficiency of information transfer and tested them against levels of [[18]F]AV-1451. Higher Tau burden in early Alzheimer's disease was associated with a shift away from the optimal small-world organization and a more fragmented network in the beta and gamma bands, whereby parieto-occipital areas were disconnected from the anterior parts of the network. Similarly, higher Tau burden was associated with decreases in both local and global efficiency, especially in the gamma band. The results support the translational development of neurophysiological "signatures" of Alzheimer's disease, to understand disease mechanisms in humans and facilitate experimental medicine studies.

Keywords: Alzheimer's disease, Connectivity, Graph theory, MEG, PET, Tau

Neurobiology of aging (2020), Vol. 92 (32280029) (18 citations)

Complexity changes in preclinical Alzheimer's disease: An MEG study of subjective cognitive decline and mild cognitive impairment (2020)

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OBJECTIVE To analyse magnetoencephalogram (MEG) signals with Lempel-Ziv Complexity (LZC) to identify the regions of the brain showing changes related to cognitive decline and Alzheimeŕs Disease (AD).

METHODS LZC was used to study MEG signals in the source space from 99 participants (36 male, 63 female, average age: 71.82 ± 4.06) in three groups (33 subjects per group): healthy (control) older adults, older adults with subjective cognitive decline (SCD), and adults with mild cognitive impairment (MCI). Analyses were performed in broadband (2-45 Hz) and in classic narrow bands (theta (4-8 Hz), alpha (8-12 Hz), low beta (12-20 Hz), high beta (20-30 Hz), and, gamma (30-45 Hz)).

RESULTS LZC was significantly lower in subjects with MCI than in those with SCD. Moreover, subjects with MCI had significantly lower MEG complexity than controls and SCD subjects in the beta frequency band. Lower complexity was correlated with smaller hippocampal volumes.

CONCLUSIONS Brain complexity - measured with LZC - decreases in MCI patients when compared to SCD and healthy controls. This decrease is associated with a decrease in hippocampal volume, a key feature in AD progression.

SIGNIFICANCE This is the first study to date characterising the changes of brain activity complexity showing the specific spatial pattern of the alterations as well as the morphological correlations throughout preclinical stages of AD.

Keywords: Alzheimer's disease, Lempel-Ziv complexity, Magnetoencephalogram, Mild cognitive impairment, Source space, Subjective cognitive decline

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 2 (31884374) (11 citations)

What electrophysiology tells us about Alzheimer's disease: a window into the synchronization and connectivity of brain neurons (2020)

Babiloni, Claudio; Blinowska, Katarzyna; Bonanni, Laura; Cichocki, Andrej; De Haan, Willem; Del Percio, Claudio; Dubois, Bruno; Escudero, Javier; Fernández, Alberto; Frisoni, Giovanni; Guntekin, Bahar; Hajos, Mihaly; Hampel, Harald; Ifeachor, Emmanuel; Kilborn, Kerry; Kumar, Sanjeev; Johnsen, Kristinn; Johannsson, Magnus; Jeong, Jaeseung; LeBeau, Fiona; Lizio, Roberta; Lopes da Silva, Fernando; Maestú, Fernando; McGeown, William J; McKeith, Ian; Moretti, Davide Vito; Nobili, Flavio; Olichney, John; Onofrj, Marco; Palop, Jorge J; Rowan, Michael; Stocchi, Fabrizio; Struzik, Zbigniew M; Tanila, Heikki; Teipel, Stefan; Taylor, John Paul; Weiergräber, Marco; Yener, Gorsev; Young-Pearse, Tracy; Drinkenburg, Wilhelmus H; Randall, Fiona

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ABSTRACT Electrophysiology provides a real-time readout of neural functions and network capability in different brain states, on temporal (fractions of milliseconds) and spatial (micro, meso, and macro) scales unmet by other methodologies. However, current international guidelines do not endorse the use of electroencephalographic (EEG)/magnetoencephalographic (MEG) biomarkers in clinical trials performed in patients with Alzheimer's disease (AD), despite a surge in recent validated evidence. This position paper of the ISTAART Electrophysiology Professional Interest Area endorses consolidated and translational electrophysiological techniques applied to both experimental animal models of AD and patients, to probe the effects of AD neuropathology (i.e., brain amyloidosis, tauopathy, and neurodegeneration) on neurophysiological mechanisms underpinning neural excitation/inhibition and neurotransmission as well as brain network dynamics, synchronization, and functional connectivity, reflecting thalamocortical and corticocortical residual capacity. Converging evidence shows relationships between abnormalities in EEG/MEG markers and cognitive deficits in groups of AD patients at different disease stages. The supporting evidence for the application of electrophysiology in AD clinical research as well as drug discovery pathways warrants an international initiative to include the use of EEG/MEG biomarkers in the main multicentric projects planned in AD patients, to produce conclusive findings challenging the present regulatory requirements and guidelines for AD studies.

Keywords: Alzheimer's disease (AD), Electroencephalography and magnetoencephalography (EEG and MEG), Event-related potentials and magnetic fields, Preclinical and clinical research, Resting-state condition, The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART)

Neurobiology of aging (2020), Vol. 85 (31739167) (77 citations)

In Vivo Assay of Cortical Microcircuitry in Frontotemporal Dementia: A Platform for Experimental Medicine Studies (2021)

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ABSTRACT The analysis of neural circuits can provide crucial insights into the mechanisms of neurodegeneration and dementias, and offer potential quantitative biological tools to assess novel therapeutics. Here we use behavioral variant frontotemporal dementia (bvFTD) as a model disease. We demonstrate that inversion of canonical microcircuit models to non-invasive human magnetoencephalography, using dynamic causal modeling, can identify the regional- and laminar-specificity of bvFTD pathophysiology, and their parameters can accurately differentiate patients from matched healthy controls. Using such models, we show that changes in local coupling in frontotemporal dementia underlie the failure to adequately establish sensory predictions, leading to altered prediction error responses in a cortical information-processing hierarchy. Using machine learning, this model-based approach provided greater case-control classification accuracy than conventional evoked cortical responses. We suggest that this approach provides an in vivo platform for testing mechanistic hypotheses about disease progression and pharmacotherapeutics.

Keywords: DCM, MEG, dementia, machine learning, microcircuitry

Cerebral cortex (New York, N.Y.: 1991) (2021), Vol. 31, No. 3 (31216360) (12 citations)

Gamma band VMPFC-PreCG.L connection variation after the onset of negative emotional stimuli can predict mania in depressive patients (2023)

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OBJECTIVE Because of the similar clinical symptoms, it is difficult to distinguish unipolar disorder (UD) from bipolar disorder (BD) in the depressive episode using the available clinical features, especially for those who meet the diagnostic criteria of UD, however, experience the manic episode during the follow-up (tBD).

METHODS Magnetoencephalography recordings during a sad expression recognition task were obtained from 81 patients (27 BD, 24 tBD, 30 UD) and 26 healthy controls (HCs). Source analysis was applied to localize 64 regions of interest in the low gamma band (30-50 Hz). Regional functional connections (FCs) were constructed respectively within three time periods (early: 0-200 ms, middle: 200-400 ms, and post: 400-600 ms). The network-based statistic method was used to explore the abnormal connection patterns in tBD compared to UD and HC. BD was applied to explore whether such abnormality is still significant between every two groups of BD, tBD, UD, and HC.

RESULTS The VMPFC-PreCG.L connection was found to be a significantly different connection between tBD and UD in the early time period and between tBD and BD in the middle time period. Furthermore, the middle/early time period ratio of FC value of VMPFC-PreCG.L connection was negatively correlated with the bipolarity index in tBD.

CONCLUSIONS The VMPFC-PreCG.L connection in different time periods after the onset of sad facial stimuli may be a potential biomarker to distinguish the different states of BD. The FC ratio of VMPFC-PreCG.L connection may predict whether patients with depressive episodes subsequently develop mania.

Keywords: Bipolar disorder, Magnetoencephalography, Network-based statistic, Unipolar disorder

Journal of psychiatric research (2023), Vol. 158 (36586215) (0 citations)

Hampered gamma oscillations induced by sad emotion underlying suicide attempt in major depressive disorder (2023)

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AIM Major depressive disorder (MDD) is associated with high suicidality, especially for those with suicide attempt (SA). Although impaired oscillatory activity has been previously reported in patients with SA, little is known about precise temporal-spatial variability of its neural dynamics. To solve this, the current study probed the spectral power and network interactions underlying SA in MDD.

METHODS The present study recruited 104 subjects including 56 subjects with MDD (30 with SA and 26 without SA) and 48 healthy controls, who performed sad expressions recognition task during magnetoencephalography (MEG) recording. By investigating source-reconstructed MEG-data, brain states representing different task stages were estimated from a Hidden Markov model. Spectrum power and network connectivity were compared via Gaussian Mixture Models, and fractional occupancy (FO) of states were compared via an independent F-test.

RESULTS Brain states were corresponding to various frequencies (theta/beta/low gamma/ high gamma). In low gamma band (35-45 Hz), the early visual state exhibited increased activation and hyper inter-network connectivity between visual regions and the limbic system, while the middle fronto-parietal state exhibited attenuated activation and decreased intra-network connectivity within fronto-parietal regions in SA group. Crucially, FO values of these two states were significantly correlated with the suicide risks.

CONCLUSIONS Suicide behavior of patients with MDD was significantly associated with aberrant oscillations in low gamma band. Elevated oscillations in occipital cortices and attenuated oscillations in fronto-parietal cortices were significantly associated with SA. Manifesting sadness indulging and reckless decision-making, the hampered temporal characteristics could help explain the neural-electric basis of SA.

Keywords: brain dynamics, gamma oscillations, major depressive disorders, negative emotional bias, suicide attempt

Psychiatry and clinical neurosciences (2023), Vol. 77, No. 1 (36207792) (1 citation)

Association between cognitive impairments and aberrant dynamism of overlapping brain sub-networks in unmedicated major depressive disorder: A resting-state MEG study (2023)

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OBJECTIVE Little is known about the pathogenesis underlying cognitive impairment in major depressive disorder (MDD). We aimed to explore the mechanisms of cognitive impairments among patients with MDD by investigating the dynamics of overlapping brain subnetworks.

METHODS Forty unmedicated patients with MDD and 28 healthy controls (HC) were enrolled in this study. Cognitive function was measured using the Chinese versions of MATRICS Consensus Cognitive Battery (MCCB). All participants were scanned using a whole-head resting-state magnetoencephalography (MEG) machine. The dynamism of neural sub-networks was analyzed based on the detection of overlapping communities in five frequency bands of oscillatory brain signals.

RESULTS MDD demonstrated poorer cognitive performance in six domains compared to HC. The difference in community detection (functional integration mode) in MDD was frequency-dependent. MDD showed significantly decreased community dynamics in all frequency bands compared to HC. Specifically, differences in the visual network (VN) and default mode network (DMN) were detected in all frequency bands, differences in the cognitive control network (CCN) were detected in the alpha2 and beta frequency bands, and differences in the bilateral limbic network (BLN) were only detected in the beta frequency band. Moreover, community dynamics in the alpha2 frequency band were positively correlated with verbal learning and reasoning problem solving abilities in MDD.

CONCLUSIONS Our study found that decreasing in the dynamics of overlapping sub-networks may differ by frequency bands. The aberrant dynamics of overlapping neural sub-networks revealed by frequency-specific MEG signals may provide new information on the mechanism of cognitive impairments that result from MDD.

Keywords: Cognitive function, Dynamic functional connectivity, Magnetoencephalography, Major depressive disorder, Overlapping sub-network

Journal of affective disorders (2023), Vol. 320 (36179776) (0 citations)

MEG-based Classification and Grad-CAM Visualization for Major Depressive and Bipolar Disorders with Semi-CNN (2022)

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ABSTRACT Major depressive disorder (MDD) and bipolar disorder (BD) are two major mood disorders with partly overlapped symptoms but different treatments. However, their misdiagnosis and mistreatment are common based on the DSM-V criteria, lacking objective and quantitative indicators. This study aimed to develop a novel approach that accurately classifies MDD and BD based on their resting-state magnetoencephalography (MEG) signals during euthymic phases. A revisited 3D CNN model, Semi-CNN, that could automatically detect brainwave patterns in spatial, temporal, and frequency domains was implemented to classify wavelet-transformed MEG signals of normal controls and MDD and BD patients. The model achieved a test accuracy of 96.05% and an average of 95.71% accuracy for 5-fold cross-validation. Furthermore, saliency maps of the model were estimated using Grad-CAM++ to visualize the proposed classification model and highlight disease-specific brain regions and frequencies. Clinical Relevance - Our model provides a stable pipeline that accurately classifies MDD, BD, and healthy individuals based on resting-state MEG signals during the euthymic phases, opening the potential for quantitative and accurate brain-based diagnosis for the highly misdiagnosed MDD/BD patients.

Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference (2022), Vol. 2022 (36086021) (0 citations)

Research on the MEG of Depression Patients Based on Multivariate Transfer Entropy (2022)

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ABSTRACT The pathogenesis of depression is complex, and the current means of medical diagnosis is single. Patients with severe depression may even have great physical pain and suicidal tendencies. Magnetoencephalography (MEG) has the characteristics of ultra-high spatiotemporal resolution and safety. It is a good medical means for the diagnosis of depression. In this paper, multivariate transfer entropy algorithm is used to study MEG of depression. In this paper, the subjects are divided into the same brain region and the multi-channel combination between different brain regions,

and the multivariate transfer entropy of patients with depression and healthy controls under different EEG signal frequency bands is calculated. Finally, the significant difference between the two groups of experimental samples is verified by the results of independent sample t-test. The experimental results show that for the same combination of brain channels, the multivariate transfer entropy in the depression group is generally lower than that in the healthy control group, and the difference is the best in γ frequency band and the largest in the frontal region.

Computational intelligence and neuroscience (2022), Vol. 2022 (35909866) (0 citations)

Alpha-beta decoupling relevant to inhibition deficits leads to suicide attempt in major depressive disorder (2022)

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BACKGROUND One devastating outcome of major depressive disorder (MDD) is high suicidality, especially for patients with suicide attempt (SA). Evidence indicated that SA may be strongly associated with inhibitory control deficits. We hypothesized that the inhibition function deficits of patient with SA might be underpinned by abnormal neuronal oscillations.

METHODS Our study recruited 111 subjects including 74 patients and 37 controls, who performed a GO/NOGO task during magnetoencephalography recording. Time-frequency-representations and phase-amplitude-coupling were measured for the brain circuits involved in the inhibitory function. Phase-slope-indexes were calculated between regions to determine the direction of power flow.

RESULTS Significant increased reaction time and decreased judgment accuracy were observed in SA group. During the perception stage of GO task (approximately 125 ms), SA group manifested elevated alpha power in ventral prefrontal cortex (VPFC) and attenuated beta power in dorsal anterior cingulate (dACC) compared with other groups ($p < 0.01$). In the processing stage of NOGO task (approximately 300 ms), they showed decreased beta power in VPFC and increased alpha power in dACC ($p < 0.01$). Alpha-beta decoupling during both tasks was observed in SA group. Furthermore, the decoupling from VPFC to dACC under NOGO tasks was significantly correlated with suicide risk level.

LIMITATIONS The number of participants was relatively small, and psychological elements were not involved in current study.

CONCLUSION Dysregulated oscillatory activities of dACC and VPFC suggested deficits in execution and inhibition functions triggering high suicide risks. The alpha-beta decoupling from VPFC to dACC could be served as a neuro-electrophysiological biomarker for identifying potential suicide risk.

Keywords: Alpha-beta coupling, GO/NOGO task, Inhibitory function, Suicide attempt

Journal of affective disorders (2022), Vol. 314 (35820473) (1 citation)

Magnetoencephalography biomarkers of suicide attempt history and antidepressant response to ketamine in treatment-resistant major depression (2022)

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BACKGROUND This study examined magnetoencephalographic (MEG) correlates of suicidal ideation (SI) and suicide attempt history in patients with treatment-resistant major depression (TRD) at baseline and following subanesthetic-dose ketamine infusion.

METHODS Twenty-nine drug-free TRD patients (12 suicide attempters/17 non-attempters) participated in a crossover randomized trial of ketamine. MEG data were collected during an attentional dot probe task with emotional face stimuli at baseline and several hours post-ketamine infusion. Synthetic aperture magnetometry was used to project source power in the theta, alpha, beta, and gamma frequencies for angry-neutral, happy-neutral, and neutral-neutral face pairings during a one-second peristimulus period. Mixed models were used to test for clinical, behavioral, and electrophysiological effects of group, emotion, session, and SI score.

RESULTS Ketamine significantly reduced SI and depression across the sample. Post-ketamine, attempters had improved accuracy and non-attempters had reduced accuracy on the task. SI was positively associated with gamma power in regions of the frontal and parietal cortices across groups. In an extended amygdala-hippocampal region, attempters differed significantly in their emotional reactivity to angry versus happy faces as indexed by theta power differences, irrespective of drug. Ketamine significantly reduced the association between alpha power and SI for angry compared with happy faces in a fronto-insular/anterior cingulate region important for regulating sensory attentiveness.

LIMITATIONS Limitations include a small sample size of attempters.

CONCLUSIONS The findings highlight key differences in band-limited power between attempters and non-attempters and reinforce previous findings that ketamine has distinct response properties in patients with a suicide history.

Keywords: Ketamine, Magnetoencephalography, Suicidal ideation, Suicide attempt, Treatment-resistant depression

Journal of affective disorders (2022), Vol. 312 (35728680) (0 citations)

Spontaneous transient states of fronto-temporal and default-mode networks altered by suicide attempt in major depressive disorder (2022)

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ABSTRACT Major depressive disorder (MDD) is associated with increased suicidality, and it's still challenging to identify suicide in clinical practice. Although suicide attempt (SA) is the most relevant precursor with multiple functional abnormalities reported from neuroimaging studies, little is known about how the spontaneous transient activated patterns organize and coordinate brain networks underlying SA. Thus, we obtained resting-state magnetoencephalography data for two MDD subgroups of 44 non-suicide patients and 34

suicide-attempted patients, together with 49 matched health-controls. For the source-space signals, Hidden Markov Model (HMM) helped to capture the sub-second dynamic activity via a hidden sequence of finite number of states. Temporal parameters and spectral activation were acquired for each state and then compared between groups. Here, HMM states characterized the spatiotemporal signatures of eight networks. The activity of suicide attempters switches more frequently into the fronto-temporal network, as the time spent occupancy of fronto-temporal state is increased and interval time is decreased compared with the non-suicide patients. Moreover, these changes are significantly correlated with Nurses' Global Assessment of Suicide Risk scores. Suicide attempters also exhibit increased state-wise activations in the theta band (4-8 Hz) in the posterior default mode network centered on posterior cingulate cortex, which can't be detected in the static spectral analysis. These alternations may disturb the time allocations of cognitive control regulations and cause inflexible decision making to SA. As the better sensitivity of dynamic study in reflecting SA diathesis than the static is validated, dynamic stability could serve as a potential neuronal marker for SA.

Keywords: Dynamics, Magnetoencephalography, Major depressive disorder, Oscillations, Resting state, Suicide

European archives of psychiatry and clinical neuroscience (2022), Vol. 272, No. 8 (35088122) (0 citations)

Investigating default mode network connectivity disruption in children of mothers with depression (2022)

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BACKGROUND Exposure to maternal major depressive disorder (MDD) bears long-term negative consequences for children's well-being; to date, no research has examined how exposure at different stages of development differentially affects brain functioning.

AIMS Utilising a unique cohort followed from birth to preadolescence, we examined the effects of early versus later maternal MDD on default mode network (DMN) connectivity.

METHOD Maternal depression was assessed at birth and ages 6 months, 9 months, 6 years and 10 years, to form three groups: children of mothers with consistent depression from birth to 6 years of age, which resolved by 10 years of age; children of mothers without depression; and children of mothers who were diagnosed with MDD in late childhood. In preadolescence, we used magnetoencephalography and focused on theta rhythms, which characterise the developing brain.

RESULTS Maternal MDD was associated with disrupted DMN connectivity in an exposure-specific manner. Early maternal MDD decreased child connectivity, presenting a profile typical of early trauma or chronic adversity. In contrast, later maternal MDD was linked with tighter connectivity, a pattern characteristic of adult depression. Aberrant DMN connectivity was predicted by intrusive mothering in infancy and lower mother-child reciprocity and child empathy in late childhood, highlighting the role of deficient caregiving and compromised socio-emotional competencies in DMN dysfunction.

CONCLUSIONS The findings pinpoint the distinct effects of early versus later maternal MDD on the DMN, a core network sustaining self-related processes. Results emphasise that research on the influence of early adversity on the developing brain should consider the developmental stage in which the adversity occured.

Keywords: Depressive disorders, aetiology, childhood experience, imaging, social functioning

The British journal of psychiatry: the journal of mental science (2022), Vol. 220, No. 3 (35049492) (2 citations)

Attenuated alpha-gamma coupling in emotional dual pathways with right-Amygdala predicting ineffective antidepressant response (2022)

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AIMS The diversity of treatment outcomes for major depressive disorder (MDD) remains uncertain in neuropathology. The current study aimed at exploring electrophysiological biomarkers associated with treatment response.

METHODS The present study recruited 130 subjects including 100 MDD patients and 30 healthy controls. All subjects participated in a sad expression recognition task while their magnetoencephalography data were recorded. Patients who had a reduction of at least 50% in disorder severity at endpoint (>2 weeks) were considered as responders. Within-frequency power and phase-amplitude coupling were measured for the brain regions involved in the emotional visual information processing pathways.

RESULTS The significant alpha-gamma decoupling from the right thalamus to the right amygdala in unconscious processing and from right orbital frontal cortices to the right amygdala in conscious processing was found in non-responders relative to responders and healthy controls. These kinds of dysregulation could also predict the potential treatment response.

CONCLUSION The attenuated alpha-gamma coupling in dual pathways indicated increased sensitivity to the negative emotional information and reduced moderated effect of the amygdala, which might cause insensitivity to antidepressant treatment and could be regarded as potential neural mechanisms for treatment response prediction.

Keywords: alpha-gamma coupling, amygdala, antidepressant response, dual pathways, magnetoencephalography, negative stimuli

CNS neuroscience & therapeutics (2022), Vol. 28, No. 3 (34953030) (3 citations)

Differences in verbal and spatial working memory in patients with bipolar II and unipolar depression: an MSI study (2021)

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BACKGROUND Depressive symptoms could be similarly expressed in bipolar and unipolar disorder. However, changes in cognition and brain networks might be quite distinct. We aimed to find out the difference in the neural mechanism of impaired working memory in patients with bipolar and unipolar disorder.

METHOD According to diagnostic criteria of bipolar II disorder of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and assessments, 13 bipolar II depression (BP II), 8 unipolar depression (UD) patients and 15 healthy controls (HC) were recruited in the study. We used 2-back tasks and magnetic source imaging (MSI) to test working memory functions and get the brain reactions of the participants.

RESULTS Compared with HC, only spatial working memory tasks accuracy was significantly worse in both UD and BP II ($p = 0.001$). Pearson correlation showed that the stronger the FCs' strength of MFG-IPL and IPL-preSMA, the higher accuracy of SWM task within left FPN in patients with UD ($r = 0.860$, $p = 0.006$; $r = 0.752$, $p = 0.031$). However, the FC strength of IFG-IPL was negatively correlated with the accuracy of SWM task within left FPN in patients with BP II ($r = -0.591$, $p = 0.033$).

CONCLUSIONS Our study showed that the spatial working memory of patients with whether UD or BP II was impaired. The patterns of FCs within these two groups of patients were different when performing working memory tasks.

Keywords: Depression, Frontoparietal network, Magnetoencephalography, Working memory

BMC psychiatry (2021), Vol. 21, No. 1 (34781922) (2 citations)

Disrupted fronto-parietal network and default-mode network gamma interactions distinguishing suicidal ideation and suicide attempt in depression (2022)

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BACKGROUND Precise suicide risk evaluation struggled in Major depressive disorder (MDD), especially for patients with only suicidal-ideation (SI) but without suicide attempt (SA). MDD patients have deficits in negative emotion processing, which is associated with the generation of SI and SA. Given the critical role of gamma oscillations in negative emotion processing, we hypothesize that the transition from SI to SA in MDD could be characterized by abnormal gamma interactions.

METHODS We recruited 162 participants containing 106 MDD patients and 56 healthy controls (HCs). Participants performed facial recognition tasks while magnetoencephalography data were recorded. Time-frequency-representation (TFR) analysis was conducted to identify the dominant spectra differences between MDD and HCs, and then source analysis was applied to localize the region of interests. Furthermore, frequency-specific functional connectivity network were constructed and a semi-supervised clustering algorithm was utilized to predict potential suicide risk.

RESULTS Gamma (50-70 Hz) power was found significantly increased in MDD, mainly residing in regions from fronto-parietal-control-network (FPN), visual-network (VN), default-mode-network (DMN) and salience-network (SN). Based on impaired gamma functional connectivity network between well-established SA group and non-SI group, semi-supervised algorithm clustered patients with only SI into two groups with different suicide risks. Moreover, Inter-network gamma connectivity between FPN and DMN significantly negatively correlated with suicide risk and not confounded by depression severity.

CONCLUSION Inter-network gamma connectivity with FPN and DMN might be the key neuropathological interactions underling the progression from SI to SA. By applying semi-supervised clustering to electrophysiological data, it is possible to predict individual suicide risk.

Keywords: Gamma band, Magnetoencephalography (MEG), Major depression, Semi-supervised clustering, Suicidal ideation, Suicide attempt

Progress in neuro-psychopharmacology & biological psychiatry (2022), Vol. 113 (34780814) (4 citations)

Sub-second transient activated patterns to sad expressions in major depressive disorders discovered via hidden Markov model (2021)

Dai, Zhongpeng; Zhang, Siqi; Wang, Xinyi; Wang, Huan; Zhou, Hongliang; Tian, Shui; Chen, Zhilu; Lu, Qing; Yao, Zhijian

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ABSTRACT The pathological mechanisms of major depressive disorders (MDDs) is associated with the overexpression of negative emotions, and the fast transient-activated patterns underlying overrepresentation in depression still remain to be revealed to date. We hypothesized that the aberrant spatiotemporal attributes of the process of sad expressions are related to the neuropathology of MDD and help to detect the depression severity. We enrolled a total of 96 subjects including 47 patients with MDD and 49 healthy controls (HCs), and recorded their magnetoencephalography data under a sad expression recognition task. A hidden Markov model (HMM) was applied to separate the whole neural activity into several brain states, then to characterize the dynamics. To find the disrupted temporal-spatial characteristics, power estimations and fractional occupancy (FO) of each state were estimated and contrasted between MDDs and HCs. Three states were found over the period of emotional stimuli processing procedure. The early visual stage (0-270 ms) was mainly manifested by state 1, and the emotional information processing stage (270-600 ms) was manifested by state 2, while the state 3 remained a steady proportion across the whole period. MDDs activated statistically more in limbic system during state 2 ($p = 0.0045$) and less in frontoparietal control network during state 3 ($p = 5.38 \times 10[-5]$) relative to HCs. Hamilton Depression Rating Scale scores were significantly correlated with the predicted disorder severity using FO values ($p = 0.0062$, $r = 0.3933$). Relative to HCs, MDDs perceived the sad contents quickly and spent more time overexpressing the negative emotions. These phenomena indicated MDD patients might easily indulge in negative emotion and neglect other things. Furthermore, temporal descriptors built by HMM could be potential biomarkers for identifying the severity of depression disorders.

Keywords: hidden Markov model, magnetoencephalography, major depressive disorders, negative stimuli

Journal of neuroscience research (2021), Vol. 99, No. 12 (34585763) (5 citations)

Increased theta/alpha synchrony in the habenula-prefrontal network with negative emotional stimuli in human patients (2021)

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ABSTRACT Lateral habenula is believed to encode negative motivational stimuli and plays key roles in the pathophysiology of psychiatric disorders. However, how habenula activities are modulated during the processing of emotional information is still poorly understood. We recorded local field potentials from bilateral habenula areas with simultaneous cortical magnetoencephalography in nine patients with psychiatric disorders during an emotional picture-viewing task. Transient activity in the theta/alpha band (5-10 Hz) within the habenula and prefrontal cortical regions, as well as the coupling between these structures, is increased during the perception and processing of negative emotional stimuli compared to positive emotional stimuli. The increase in theta/alpha band synchronization in the frontal cortex-habenula network correlated with the emotional valence but not the arousal score of the stimuli. These results provide direct evidence for increased theta/alpha synchrony within the habenula area and prefrontal cortex-habenula network in the perception of negative emotion in human participants.

Keywords: deep brain stimulation, depression, emotional stimuli, habenula, human, neuroscience, prefrontal cortex-habenula network, theta / alpha oscillations

eLife (2021), Vol. 10 (34251338) (4 citations)

Acute effect of vagus nerve stimulation (VNS) on brain function (2021)

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INTRODUCTION VNS is a non-pharmalogical neuromodulatory treatment option for difficult-to-treat depression. A pulse generator implanted in the left chest area is connected to an electrode that is wrapped around the left vagal nerve. It is presumed, that the vagal afferent network modulates neuronal activity in key monoaminergic structures.

METHODS We performed MEG recording during active stimulation of the left vagal nerve. Our patient was a 60 years old female treated with VNS since December 2019 due to unipolar major depression.

RESULTS MEG recording and analysis were possible despite stimulation signals and the metal stimulation systems. We saw a reproducible reduction of the 10-Hz-alpha amplitude after the end of the 30 s stimulation period in wide-spread areas including parieto-occipital cortex where alpha oscillations are prominently generated. During stimulation, however, alpha oscillations remained unaffected. These findings could be reproduced in a second measurement.

CONCLUSION Increased alpha power was linked to depressive states and alterations of cortical activity. A reduction may indicate cortical activation by stimulation of the vagal nerve as a possible mechanism of action of VNS in depression.

Keywords: DTD, Difficult-to-treat depression, MEG, Magnetoencephalography, TRD, Treatment-resistant depression, VNS, Vagus nerve stimulation

Journal of psychiatric research (2021), Vol. 141 (34198194) (3 citations)

Ketamine Alters Electrophysiological Responses to Emotional Faces in Major Depressive Disorder (2021)

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BACKGROUND The glutamatergic modulator ketamine rapidly reduces depressive symptoms in individuals with treatment-resistant major depressive disorder (MDD). However, ketamine's effects on emotional processing biases remain largely unknown, and understanding these processes may help elucidate ketamine's mechanism of action.

METHODS Magnetoencephalography (MEG) was used to investigate ketamine's effects on early visual responses to affective stimuli in individuals with MDD (n=31) and healthy volunteers (HVs; n=24). Participants were enrolled in a double-blind, placebo-controlled, crossover clinical trial and were assessed at baseline and after subanesthetic-dose ketamine and placebo-saline infusions. During MEG recording, participants completed an emotional evaluation task in which they indicated the sex or emotional valence (happy-neutral or sad-angry) of facial stimuli. Source-localized event-related field (ERF) M100 and M170 amplitudes and latencies were extracted from regions of interest. Linear fixed effects models examined interactions between diagnosis, stimulus valence, and drug session for behavioral and MEG data.

RESULTS In baseline behavioral analyses, MDD participants exhibited higher accuracy for sad-angry than happy-neutral faces, and HVs responded faster to happy-neutral than sad-angry faces. In the MEG post-infusion analyses, calcarine M100 amplitudes were larger in MDD than HV participants post-placebo but became more similar post-ketamine. Finally, fusiform M170 amplitudes were associated with antidepressant response in MDD participants.

LIMITATIONS The modest sample size and the need to collapse across responses to happy and neutral faces to increase statistical power limit the generalizability of the findings.

CONCLUSIONS Ketamine rapidly altered emotional stimulus processing in MDD, laying the groundwork for future investigations of biomarkers of antidepressant treatment response.

CLINICAL TRIAL Clinicaltrials.gov, NCT#00088699.

Keywords: depression, emotional face processing, ketamine, magnetoencephalography

Journal of affective disorders (2021), Vol. 279 (33074143) (3 citations)

Troubled Hearts: Association Between Heart Rate Variability and Depressive Symptoms in Healthy Children (2020)

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ABSTRACT Heart rate variability (HRV) captures the change in timing of consecutive heart beats and is reduced in individuals with depression and anxiety. The present study investigated whether typically-developing children without clinically recognized signs of depression or anxiety showed a relationship between HRV and depressive or anxiety symptoms. Children aged 9-14 years (N = 104) provided three minutes of cardiac signal during eyes closed rest and eyes open rest. The association between high frequency HRV, low frequency HRV, root mean square of the successive differences (RMSSD), and pNN20 versus depressive symptoms (NIH Toolbox and Child Behavior Checklist) was investigated. Results partially confirm our hypothesis, with pNN20 positively correlated with the self-reported depression measure of loneliness while controlling for age, sex, social status, and physical activity. The association was stronger in male participants. However, there is no consensus in the literature about which HRV measures are associated with depressive symptoms in healthy children. Additional studies are needed which reliably account for variables that influence HRV to establish whether certain HRV measures can be used as an early marker for depression risk in children.

Keywords: Depression, Healthy children, Heart rate variability, Loneliness, RMSSD, pNN20

Applied psychophysiology and biofeedback (2020), Vol. 45, No. 4 (32978742) (0 citations)

Multilayer MEG functional connectivity as a potential marker for suicidal thoughts in major depressive disorder (2020)

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ABSTRACT Major depressive disorder (MDD) is highly heterogeneous in its clinical presentation. The present exploratory study used magnetoencephalography (MEG) to investigate electrophysiological intrinsic connectivity differences between healthy volunteers and unmedicated participants with treatment-resistant MDD. The study examined canonical frequency bands from delta through gamma. In addition to group comparisons, correlational studies were conducted to determine whether connectivity was related to five symptom factors: depressed mood, tension, negative cognition, suicidal thoughts, and amotivation. The MDD and healthy volunteer groups did not differ significantly at baseline when corrected across all frequencies and clusters, although evidence of generalized slowing in MDD was observed. Notably, however, electrophysiological connectivity was strongly related to suicidal thoughts, particularly as coupling of low frequency power fluctuations (delta and theta) with alpha and beta power. This analysis revealed hub areas underlying this symptom cluster, including left hippocampus, left anterior insula, and bilateral dorsolateral prefrontal cortex. No other symptom cluster demonstrated a relationship with neurophysiological connectivity, suggesting a specificity to these results as markers of suicidal ideation.

Keywords: Connectivity, Frequency, Magnetoencephalography, Major depressive disorder, Oscillation, Suicide

NeuroImage. Clinical (2020), Vol. 28 (32836087) (8 citations)

Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression (2020)

Farmer, Cristan A; Gilbert, Jessica R; Moaddel, Ruin; George, Jomy; Adeojo, Lilian; Lovett, Jacqueline;

Nugent, Allison C; Kadriu, Bashkim; Yuan, Peixiong; Gould, Todd D; Park, Lawrence T; Zarate, Carlos A

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ABSTRACT A single, subanesthetic dose of (R,S)-ketamine (ketamine) exerts rapid and robust antidepressant effects. Several groups previously reported that (2S,6S;2R,6R)-hydroxynorketamine (HNK) had antidepressant effects in rodents, and that (2R,6R)-HNK increased cortical electroencephalographic gamma power. This exploratory study examined the relationship between ketamine metabolites, clinical response, psychotomimetic symptoms, and gamma power changes in 34 individuals (ages 18-65) with treatment-resistant depression (TRD) who received a single ketamine infusion (0.5 mg/kg) over 40 min. Plasma concentrations of ketamine, norketamine, and HNKs were measured at 40, 80, 120, and 230 min and at 1, 2, and 3 days post-infusion. Linear mixed models evaluated ketamine metabolites as mediators of antidepressant and psychotomimetic effects and their relationship to resting-state whole-brain magnetoencephalography (MEG) gamma power 6-9 h post-infusion. Three salient findings emerged. First, ketamine concentration positively predicted distal antidepressant response at Day 11 post-infusion, and an inverse relationship was observed between (2S,6S;2R,6R)-HNK concentration and antidepressant response at 3 and 7 days post-infusion. Norketamine concentration was not associated with antidepressant response. Second, ketamine, norketamine, and (2S,6S;2R,6R)-HNK concentrations at 40 min were positively associated with contemporaneous psychotomimetic symptoms; post-hoc analysis revealed that ketamine was the predominant contributor. Third, increased (2S,6S;2R,6R)-HNK maximum observed concentration (Cmax) was associated with increased MEG gamma power. While contrary to preclinical observations and our a priori hypotheses, these exploratory results replicate those of a recently published study documenting a relationship between higher (2S,6S;2R,6R)-HNK concentrations and weaker antidepressant response in humans and provide further rationale for studying gamma power changes as potential biomarkers of antidepressant response.

Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology (2020), Vol. 45, No. 8 (32252062) (32 citations)

Magnetoencephalographic Correlates of Suicidal Ideation in Major Depression (2020)

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BACKGROUND Defining the neurobiological underpinnings of suicidal ideation (SI) is crucial to improving our understanding of suicide. This study used magnetoencephalographic gamma power as a surrogate marker for population-level excitation-inhibition balance to explore the underlying neurobiology of SI and depression. In addition, effects of pharmacological intervention with ketamine, which has been shown to rapidly reduce SI and depression, were assessed.

METHODS Data were obtained from 29 drug-free patients with major depressive disorder who participated in an experiment comparing subanesthetic ketamine (0.5 mg/kg) with a placebo saline infusion. Magnetoencephalographic recordings were collected at baseline and after ketamine and placebo infusions. During scanning, patients rested with their eyes closed. SI and depression were assessed, and a linear mixed-effects model was used to identify brain regions where gamma

power and both SI and depression were associated. Two regions of the salience network (anterior insula, anterior cingulate) were then probed using dynamic causal modeling to test for ketamine effects.

RESULTS Clinically, patients showed significantly reduced SI and depression after ketamine administration. In addition, distinct regions in the anterior insula were found to be associated with SI compared with depression. In modeling of insula-anterior cingulate connectivity, ketamine lowered the membrane capacitance for superficial pyramidal cells. Finally, connectivity between the insula and anterior cingulate was associated with improvements in depression symptoms.

CONCLUSIONS These findings suggest that the anterior insula plays a key role in SI, perhaps via its role in salience detection. In addition, transient changes in superficial pyramidal cell membrane capacitance and subsequent increases in cortical excitability might be a mechanism through which ketamine improves SI.

Keywords: Depression, Gamma, Insula, Ketamine, Magnetoencephalography, Suicidal ideation

Biological psychiatry. Cognitive neuroscience and neuroimaging (2020), Vol. 5, No. 3 (31928949) (9 citations)

Magnetoencephalography resting-state spectral fingerprints distinguish bipolar depression and unipolar depression (2020)

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OBJECTIVES In clinical practice, bipolar depression (BD) and unipolar depression (UD) appear to have similar symptoms, causing BD being frequently misdiagnosed as UD, leading to improper treatment decision and outcome. Therefore, it is in urgent need of distinguishing BD from UD based on clinical objective biomarkers as early as possible. Here, we aimed to integrate brain neuroimaging data and an advanced machine learning technique to predict different types of mood disorder patients at the individual level.

METHODS Eyes closed resting-state magnetoencephalography (MEG) data were collected from 23 BD, 30 UD, and 31 healthy controls (HC). Individual power spectra were estimated by Fourier transform, and statistic spectral differences were assessed via a cluster permutation test. A support vector machine classifier was further applied to predict different mood disorder types based on discriminative oscillatory power.

RESULTS Both BD and UD showed decreased frontal-central gamma/beta ratios comparing to HC, in which gamma power (30-75 Hz) was decreased in BD while beta power (14-30 Hz) was increased in UD vs HC. The support vector machine model obtained significant high classification accuracies distinguishing three groups based on mean gamma and beta power (BD: 79.9%, UD: 81.1%, HC: 76.3%, $P < .01$).

CONCLUSIONS In combination with resting-state MEG data and machine learning technique, it is possible to make an individual and objective prediction for mode disorder types, which in turn has implications for diagnosis precision and treatment decision of mood disorder patients.

Keywords: MEG, bipolar depression, resting state, support vector machine, unipolar depression

Bipolar disorders (2020), Vol. 22, No. 6 (31729112) (9 citations)

Association between increased theta cordance and early response to ECT in late-life depression (2020)

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OBJECTIVES More than half of patients with major depression who do not respond to initial antidepressants become treatment resistant (TRD), and while electroconvulsive therapy (ECT) is effective, it involves anesthesia and other medical risks that are of concern in geriatric patients. Past studies have suggested that theta cordance (TC), a correlate of cerebral metabolism measured by electroencephalography, could guide treatment decisions related to patient selection and engagement of the therapeutic target.

METHODS/DESIGN Eight patients with late-life treatment resistant depression (LL-TRD) underwent magnetoencephalography (MEG) at baseline and following seven sessions of ECT. We tested whether the mean and regional frontal cortex TC were able to differentiate early responders from nonresponders.

RESULTS Five patients whose depression severity decreased by >30% after seven sessions were considered early responders. We found no baseline differences in mean frontal TC between early responders compared with nonresponders, but early responders exhibited a significant increase in TC following ECT. Further, we found that compared with nonresponders, early responders exhibited a greater change in TC specifically within the right prefrontal cortex.

CONCLUSIONS These results support the hypothesis that increases in frontal TC are associated with antidepressant response. We expand on previous findings by showing that this change is specific to the right prefrontal cortex. Validation of this neural marker could contribute to improved ECT outcomes, by informing early clinical decisions about the acute efficacy of this treatment.

Keywords: ECT, depression, late life, neural marker, theta cordance

International journal of geriatric psychiatry (2020), Vol. 35, No. 2 (31617234) (5 citations)

Caudothalamic dysfunction in drug-free suicidally depressed patients: an MEG study (2020)

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ABSTRACT Major depressive disorder (MDD), characterized by low mood or anhedonia, is commonly associated with a greater suicidal susceptibility. There are numerous suicide-related findings pertaining to the dorsolateral prefrontal cortex (DLPFC), caudate nucleus and thalamus, which form a cortico-striato-thalamo-cortical (CSTC) circuit responsible for executive function and working memory. An aberrant CSTC circuitry is hypothesized to be implicated in depressed patients with a high suicidal risk. 27 MDD patients were assessed with the Nurses Global Assessment of Suicide Risk (NGASR), following which 14 patients were classified into a high suicide risk group (NGASR ≥ 12) and 13 patients were assigned to a low suicide risk group (NGASR < 6). All 27 patients were enrolled with 25 healthy controls for resting-state magnetoencephalography (MEG). Cross-frequency coupling (CFC) measured the phase of alpha-band (8-13 Hz) as it modulated to

cortical gamma-band (30-48 Hz). There was a significantly lower alpha-to-gamma phase-amplitude coupling (PAC) between the right caudate and left thalamus in high-risk suicide group compared to both the low-risk suicide group and healthy controls. The presence of a weaker coupling between the right caudate and left thalamus is indicative of a caudothalamic abnormality in suicidally depressed patients. This implies that a disruption of CSTC loop could result in executive dysfunction and working memory impairment, leading to an increased suicidal risk in MDD patients. In the future, this preliminary study has the possibility of being replicated on a larger scale, and hence validates caudothalamic dysfunction as a reliable neuroimaging biomarker for suicide in depression.

Keywords: Cortico-striato-thalamo-cortical (CSTC) circuit, Cross-frequency coupling (CFC), Magnetoencephalography (MEG), Major depressive disorder (MDD), Nurses global assessment of suicide risk (NGASR)

European archives of psychiatry and clinical neuroscience (2020), Vol. 270, No. 2 (30552507) (13 citations)

Dyslexia

Neural sampling of the speech signal at different timescales by children with dyslexia (2022)

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ABSTRACT Phonological difficulties characterize individuals with dyslexia across languages. Currently debated is whether these difficulties arise from atypical neural sampling of (or entrainment to) auditory information in speech at slow rates (<10 Hz, related to speech rhythm), faster rates, or neither. MEG studies with adults suggest that atypical sampling in dyslexia affects faster modulations in the neurophysiological gamma band, related to phoneme-level representation. However, dyslexic adults have had years of reduced experience in converting graphemes to phonemes, which could itself cause atypical gamma-band activity. The present study was designed to identify specific linguistic timescales at which English children with dyslexia may show atypical entrainment. Adopting a developmental focus, we hypothesized that children with dyslexia would show atypical entrainment to the prosodic and syllable-level information that is exaggerated in infant-directed speech and carried primarily by amplitude modulations <10 Hz. MEG was recorded in a naturalistic story-listening paradigm. The modulation bands related to different types of linguistic information were derived directly from the speech materials, and lagged coherence at multiple temporal rates spanning 0.9-40 Hz was computed. Group differences in lagged speech-brain coherence between children with dyslexia and control children were most marked in neurophysiological bands corresponding to stress and syllable-level information (<5 Hz in our materials), and phoneme-level information (12-40 Hz). Functional connectivity analyses showed network differences between groups in both hemispheres, with dyslexic children showing significantly reduced global network efficiency. Global network efficiency correlated with dyslexic children's oral language development and with control children's reading development. These developmental data suggest that dyslexia is characterized by atypical neural sampling of auditory information at slower rates. They also throw new light on the nature of the gamma band temporal sampling differences reported in MEG dyslexia studies with adults.

Keywords: Dyslexia, Magnetoencephalography, Neural oscillations, Phonological deficit, Speech processing

NeuroImage (2022), Vol. 253 (35278708) (3 citations)

The role of reading experience in atypical cortical tracking of speech and speech-in-noise in dyslexia (2022)

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ABSTRACT Dyslexia is a frequent developmental disorder in which reading acquisition is delayed and that is usually associated with difficulties understanding speech in noise. At the neuronal level, children with dyslexia were reported to display abnormal cortical tracking of speech (CTS) at phrasal rate. Here, we aimed to determine if abnormal tracking relates to reduced reading experience, and if it is modulated by the severity of dyslexia or the presence of acoustic noise. We included 26 school-age children with dyslexia, 26 age-matched controls and 26 reading-level matched controls. All were native French speakers. Children's brain activity was recorded with magnetoencephalography while they listened to continuous speech in noiseless and multiple noise conditions. CTS values were compared between groups, conditions and hemispheres, and also within groups, between children with mild and severe dyslexia. Syllabic CTS was significantly reduced in the right superior temporal gyrus in children with dyslexia compared with controls matched for age but not for reading level. Severe dyslexia was characterized by lower rapid automatized naming (RAN) abilities compared with mild dyslexia, and phrasal CTS lateralized to the right hemisphere in children with mild dyslexia and all control groups but not in children with severe dyslexia. Finally, an alteration in phrasal CTS was uncovered in children with dyslexia compared with age-matched controls in babble noise conditions but not in other less challenging listening conditions (non-speech noise or noiseless conditions); no such effect was seen in comparison with reading-level matched controls. Overall, our results confirmed the finding of altered neuronal basis of speech perception in noiseless and babble noise conditions in dyslexia compared with age-matched peers. However, the absence of alteration in comparison with reading-level matched controls demonstrates that such alterations are associated with reduced reading level, suggesting they are merely driven by reduced reading experience rather than a cause of dyslexia. Finally, our result of altered hemispheric lateralization of phrasal CTS in relation with altered RAN abilities in severe dyslexia is in line with a temporal sampling deficit of speech at phrasal rate in dyslexia.

Keywords: Cortical tracking of speech, Dyslexia, MEG, Speech in noise

NeuroImage (2022), Vol. 253 (35259526) (2 citations)

Reduced Theta Sampling in Infants at Risk for Dyslexia across the Sensitive Period of Native Phoneme Learning (2022)

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ABSTRACT Research on children and adults with developmental dyslexia-a specific difficulty in learning to read and spell-suggests that phonological deficits in dyslexia are linked to basic auditory deficits in temporal sampling. However, it remains undetermined whether such deficits are already present in infancy, especially during the sensitive period when the auditory system specializes in native phoneme perception. Because dyslexia is strongly hereditary, it is possible to examine infants for early predictors of the condition before detectable symptoms emerge. This study examines low-level auditory temporal sampling in infants at risk for dyslexia across the sensitive period of native phoneme learning. Using magnetoencephalography (MEG), we found deficient auditory sampling at theta in at-risk infants at both 6 and 12 months, indicating atypical auditory sampling at the syllabic rate in those infants across the sensitive period for native-language phoneme learning. This interpretation is supported by our additional finding that auditory sampling at theta predicted later vocabulary comprehension, nonlinguistic communication and the ability to combine words. Our results indicate a possible early marker of risk for dyslexia.

Keywords: MEG, auditory, dyslexia, infant, temporal sampling

International journal of environmental research and public health (2022), Vol. 19, No. 3 (35162202) (1 citation)

Categorical perception and influence of attention on neural consistency in response to speech sounds in adults with dyslexia (2022)

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ABSTRACT Developmental dyslexia is a common neurodevelopmental disorder that is associated with alterations in the behavioral and neural processing of speech sounds, but the scope and nature of that association is uncertain. It has been proposed that more variable auditory processing could underlie some of the core deficits in this disorder. In the current study, magnetoencephalography (MEG) data were acquired from adults with and without dyslexia while they passively listened to or actively categorized tokens from a /ba/-/da/ consonant continuum. We observed no significant group difference in active categorical perception of this continuum in either of our two behavioral assessments. During passive listening, adults with dyslexia exhibited neural responses that were as consistent as those of typically reading adults in six cortical regions associated with auditory perception, language, and reading. However, they exhibited significantly less consistency in the left supramarginal gyrus, where greater inconsistency correlated significantly with worse decoding skills in the group with dyslexia. The group difference in the left supramarginal gyrus was evident only when neural data were binned with a high temporal resolution and was only significant during the passive condition. Interestingly, consistency significantly improved in both groups during active categorization versus passive listening. These findings suggest that adults with dyslexia exhibit typical levels of neural consistency in response to speech sounds with the exception of the left supramarginal gyrus and that this consistency increases during active versus passive perception of speech sounds similarly in the two groups.

Keywords: Attention, Auditory, MEG, Representation, Temporal precision, Variability

Annals of dyslexia (2022), Vol. 72, No. 1 (34495457) (1 citation)

Neural entrainment to speech and nonspeech in dyslexia: Conceptual replication and extension of previous investigations (2021)

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ABSTRACT Whether phonological deficits in developmental dyslexia are associated with impaired neural sampling of auditory information is still under debate. Previous findings suggested that dyslexic participants showed atypical neural entrainment to slow and/or fast temporal modulations in speech, which might affect prosodic/syllabic and phonemic processing respectively. However, the large methodological variations across these studies do not allow us to draw clear conclusions on the nature of the entrainment deficit in dyslexia. Using magnetoencephalography, we measured neural entrainment to nonspeech and speech in both groups. We first aimed to conceptually replicate previous studies on auditory entrainment in dyslexia, using the same measurement methods as in previous studies, and also using new measurement methods (cross-correlation analyses) to better characterize the synchronization between stimulus and brain response. We failed to observe any of the significant group differences that had previously been reported in delta, theta and gamma frequency bands, whether using speech or nonspeech stimuli. However, when analyzing amplitude cross-correlations between noise stimuli and brain responses, we found that control participants showed larger responses than dyslexic participants in the delta range in the right hemisphere and in the gamma range in the left hemisphere. Overall, our results are weakly consistent with the hypothesis that dyslexic individuals show an atypical entrainment to temporal modulations. Our attempt at replicating previously published results highlights the multiple weaknesses of this research area, particularly low statistical power due to small sample size, and the lack of methodological standards inducing considerable heterogeneity of measurement and analysis methods across studies.

Keywords: Auditory processing, Dyslexia, Magnetoencephalography, Neural oscillations, Speech

Cortex; a journal devoted to the study of the nervous system and behavior (2021), Vol. 137 (33618156) (7 citations)

Auditory deficits in infants at risk for dyslexia during a linguistic sensitive period predict future language (2021)

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ABSTRACT Developmental dyslexia, a specific difficulty in learning to read and spell, has a strong hereditary component, which makes it possible to examine infants for early predictors of the condition even prior to the emergence of detectable symptoms. Using magnetoencephalography (MEG), we found smaller and shorter neural responses to simple sounds in infants at risk for dyslexia at 6 as compared to 12 months of age, a pattern that was reversed in age-matched controls. The findings indicate atypical auditory processing in at-risk infants across the sensitive period for native-language phoneme learning. This pattern was robust and localized to the same cortical areas regardless of the modeling parameters/algorithms used to estimate the current distribution underlying the measured activity. Its localization to left temporal and left frontal brain regions indicates a potential impact of atypical auditory processing on early language learning and later lan-

guage skills because language functions are typically lateralized to the left hemisphere. This interpretation is supported by our further finding that atypical auditory responses in at-risk infants consistently predicted syntactic processing between 18 and 30 months and word production at 18 and 21 months of age. These results suggest a possible early marker of risk for dyslexia in at-risk infants.

Keywords: Auditory, Dyslexia, Infant, MEG, Marker

NeuroImage. Clinical (2021), Vol. 30 (33581583) (5 citations)

Children at risk for dyslexia show deficient left-hemispheric memory representations for new spoken word forms (2021)

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ABSTRACT Developmental dyslexia is a specific learning disorder with impairments in reading and spelling acquisition. Apart from literacy problems, dyslexics show inefficient speech encoding and deficient novel word learning, with underlying problems in phonological processing and learning. These problems have been suggested to be related to deficient specialization of the left hemisphere for language processing. To examine this possibility, we tracked with magnetoencephalography (MEG) the activation of the bilateral temporal cortices during formation of neural memory traces for new spoken word forms in 7-8-year-old children with high familial dyslexia risk and in controls. The at-risk children improved equally to their peers in overt repetition of recurring new word forms, but were poorer in explicit recognition of the recurring word forms. Both groups showed reduced activation for the recurring word forms 400-1200 ms after word onset in the right auditory cortex, replicating the results of our previous study on typically developing children (Nora et al., 2017, Children show right-lateralized effects of spoken word-form learning. PLoS ONE 12(2): e0171034). However, only the control group consistently showed a similar reduction of activation for recurring word forms in the left temporal areas. The results highlight the importance of left-hemispheric phonological processing for efficient phonological representations and its disruption in dyslexia.

Keywords: Dyslexia, Magnetoencephalography, Phonological learning, Reading acquisition

NeuroImage (2021), Vol. 229 (33454404) (3 citations)

Impaired neural response to speech edges in dyslexia (2021)

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ABSTRACT Speech comprehension has been proposed to critically rely on oscillatory cortical tracking, that is, phase alignment of neural oscillations to the slow temporal modulations (envelope) of speech. Speech-brain entrainment is readjusted over time as transient events (edges) in speech lead to speech-brain phase realignment. Auditory behavioral research suggests that phonological deficits in dyslexia are linked to difficulty in discriminating speech edges. Importantly, research to date has not specifically examined neural responses to

speech edges in dyslexia. In the present study, we used MEG to record brain activity from normal and dyslexic readers while they listened to speech. We computed phase locking values (PLVs) to evaluate phase entrainment between neural oscillations and the speech envelope time-locked to edge onsets. In both groups, we observed that edge onsets induced phase resets in the auditory oscillations tracking speech, thereby enhancing their entrainment to speech. Importantly, dyslexic readers showed weaker PLVs compared to normal readers in left auditory regions from ~.15 sec to ~.65 sec after edge onset. Our results indicate that the neural mechanism that adapts cortical entrainment to the speech envelope is impaired in dyslexia. These findings here are consistent with the temporal sampling theory of developmental dyslexia.

Keywords: Dyslexia, Magnetoencephalography, Neural oscillations, Phonological deficit, Speech

Cortex; a journal devoted to the study of the nervous system and behavior (2021), Vol. 135 (33387899) (11 citations)

Atypical MEG inter-subject correlation during listening to continuous natural speech in dyslexia (2020)

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ABSTRACT Listening to speech elicits brain activity time-locked to the speech sounds. This so-called neural entrainment to speech was found to be atypical in dyslexia, a reading impairment associated with neural speech processing deficits. We hypothesized that the brain responses of dyslexic vs. normal readers to real-life speech would be different, and thus the strength of inter-subject correlation (ISC) would differ from that of typical readers and be reflected in reading-related measures. We recorded magnetoencephalograms (MEG) of 23 dyslexic and 21 typically-reading adults during listening to ~10 min of natural Finnish speech consisting of excerpts from radio news, a podcast, a self-recorded audiobook chapter and small talk. The amplitude envelopes of band-pass-filtered MEG source signals were correlated between subjects in a cortically-constrained source space in six frequency bands. The resulting ISCs of dyslexic and typical readers were compared with a permutation-based t-test. Neuropsychological measures of phonological processing, technical reading, and working memory were correlated with the ISCs utilizing the Mantel test. During listening to speech, ISCs were mainly reduced in dyslexic compared to typical readers in delta (0.5-4 Hz) and high gamma (55-90 Hz) frequency bands. In the theta (4-8 Hz), beta (12-25 Hz), and low gamma (25-45 Hz) bands, dyslexics had enhanced ISCs to speech compared to controls. Furthermore, we found that ISCs across both groups were associated with phonological processing, technical reading, and working memory. The atypical ISCs to natural speech in dyslexics supports the temporal sampling deficit theory of dyslexia. It also suggests over-synchronization to phoneme-rate information in speech, which could indicate more effort-demanding sampling of phonemes from speech in dyslexia. These irregularities in parsing speech are likely some of the complex neural factors contributing to dyslexia. The associations between neural coupling and reading-related skills further support this notion.

Keywords: Dyslexia, Inter-subject correlation, Magnetoencephalography, Natural speech, Reading skills

NeuroImage (2020), Vol. 216 (32294536) (9 citations)

Epilepsy

Neuroimaging in Adults and Children With Epilepsy (2023)

Passaro, Erasmo A

OBJECTIVE This article discusses the fundamental importance of optimal epilepsy imaging using the International League Against Epilepsy-endorsed Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS) protocol and the use of multimodality imaging in the evaluation of patients with drug-resistant epilepsy. It outlines a methodical approach to evaluating these images, particularly in the context of clinical information.

LATEST DEVELOPMENTS Epilepsy imaging is rapidly evolving, and a high-resolution epilepsy protocol MRI is essential in evaluating newly diagnosed, chronic, and drug-resistant epilepsy. The article reviews the spectrum of relevant MRI findings in epilepsy and their clinical significance. Integrating multimodality imaging is a powerful tool in the presurgical evaluation of epilepsy, particularly in "MRI-negative" cases. For example, correlation of clinical phenomenology, video-EEG with positron emission tomography (PET), ictal subtraction single-photon emission computerized tomography (SPECT), magnetoencephalography (MEG), functional MRI, and advanced neuroimaging such as MRI texture analysis and voxel-based morphometry enhances the identification of subtle cortical lesions such as focal cortical dysplasias to optimize epilepsy localization and selection of optimal surgical candidates.

ESSENTIAL POINTS The neurologist has a unique role in understanding the clinical history and seizure phenomenology, which are the cornerstones of neuroanatomic localization. When integrated with advanced neuroimaging, the clinical context has a profound impact on identifying subtle MRI lesions or finding the "epileptogenic" lesion when multiple lesions are present. Patients with an identified lesion on MRI have a 2.5-fold improved chance of achieving seizure freedom with epilepsy surgery compared with those without a lesion. This clinical-radiographic integration is essential to accurate classification, localization, determination of long-term prognosis for seizure control, and identification of candidates for epilepsy surgery to reduce seizure burden or attain seizure freedom.

Continuum (Minneapolis, Minn.) (2023), Vol. 29, No. 1 (36795875) (0 citations)

Comparison of beamformer and ICA for dynamic connectivity analysis: A simultaneous MEG-SEEG study (2023)

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ABSTRACT Magnetoencephalography (MEG) is a powerful tool for estimating brain connectivity with both good spatial and temporal resolution. It is particularly helpful in epilepsy to characterize non-invasively the epileptic networks. However, using MEG to map brain networks requires solving a difficult inverse problem that introduces uncertainty in the activity localization and connectivity measures. Our goal here was

to compare independent component analysis (ICA) followed by dipole source localization and the linearly constrained minimum-variance beamformer (LCMV-BF) for characterizing regions with interictal epileptic activity and their dynamic connectivity. After a simulation study, we compared ICA and LCMV-BF results with intracerebral EEG (stereotaxic EEG, SEEG) recorded simultaneously in 8 epileptic patients, which provide a unique 'ground truth' to which non-invasive results can be confronted. We compared the signal time courses extracted applying ICA and LCMV-BF on MEG data to that of SEEG, both for the actual signals and the dynamic connectivity computed using cross-correlation (evolution of links in time). With our simulations, we illustrated the different effect of the temporal and spatial correlation among sources on the two methods. While ICA was more affected by the temporal correlation but robust against spatial configurations, LCMV-BF showed opposite behavior. Moreover, ICA seems more suited to retrieve the simulated networks. In case of real patient data, good MEG/SEEG correlation and good localization were obtained in 6 out of 8 patients. In 4 of them ICA had the best performance (higher correlation, lower localization distance). In terms of dynamic connectivity, the evolution in time of the cross-correlation links could be retrieved in 5 patients out of 6, however, with more variable results in terms of correlation and distance. In two patients LCMV-BF had better results than ICA. In one patient the two methods showed equally good outcomes, and in the remaining two patients ICA performed best. In conclusion, our results obtained by exploiting simultaneous MEG/SEEG recordings suggest that ICA and LCMV-BF have complementary qualities for retrieving the dynamics of interictal sources and their network interactions.

Keywords: Beamformer, Brain connectivity, Epileptic network, ICA, MEG, Simultaneous recordings, Source reconstruction

NeuroImage (2023), Vol. 265 (36513288) (0 citations)

Novel noninvasive identification of patient-specific epileptic networks in focal epilepsies: Linking single-photon emission computed tomography perfusion during seizures with resting-state magnetoencephalography dynamics (2023)

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ABSTRACT Single-photon emission computed tomography (SPECT) during seizures and magnetoencephalography (MEG) during the interictal state are noninvasive modalities employed in the localization of the epileptogenic zone in patients with drug-resistant focal epilepsy (DRFE). The present study aims to investigate whether there exists a preferentially high MEG functional connectivity (FC) among those regions of the brain that exhibit hyperperfusion or hypoperfusion during seizures. We studied MEG and SPECT data in 30 consecutive DRFE patients who had resective epilepsy surgery. We parcellated each ictal perfusion map into 200 regions of interest (ROIs) and generated ROI time series using source modeling of MEG data. FC between ROIs was quantified using coherence and phase-locking value. We defined a generalized linear model to relate the connectivity of each ROI, ictal perfusion z score, and distance between ROIs. We compared the coefficients relating perfusion z score to FC of each ROI and estimated the connectivity within and between resected and unresected ROIs. We found that perfusion z scores were strongly correlated with the FC of hyper-, and separately, hypoperfused ROIs across patients. High interictal connectivity was observed between hyperperfused brain regions inside and outside the resected area. High connectivity was also observed between regions of ictal hypoperfusion. Importantly, the ictally hypoperfused regions had a low interictal connectivity to regions that became hyperperfused during

seizures. We conclude that brain regions exhibiting hyperperfusion during seizures highlight a preferentially connected interictal network, whereas regions of ictal hypoperfusion highlight a separate, discrete and interconnected, interictal network.

Keywords: MEG, SPECT, cerebral blood perfusion, epilepsy, functional connectivity

Human brain mapping (2023), Vol. 44, No. 4 (36480260) (1 citation)

Recording of Ictal Epileptic Activity Using on-Scalp Magnetoencephalography (2023)

Feys, Odile; Corvilain, Pierre; Van Hecke, Audrey; Sculier, Claudine; Rikir, Estelle; Legros, Benjamin; Gaspard, Nicolas; Leurquin-Sterk, Gil; Holmes, Niall; Brookes, Matthew; Goldman, Serge; Wens, Vincent; De Tiège, Xavier

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Annals of neurology (2023), Vol. 93, No. 2 (36480016) (0 citations)

Clinical significance of ictal magnetoencephalography in patients undergoing epilepsy surgery (2023)

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OBJECTIVE The significance of ictal magnetoencephalography (MEG) is not well appreciated. We evaluated the relationships between ictal MEG, MRI, intracranial electroencephalography (ICEEG), surgery and postoperative seizure outcome.

METHODS A total of 45 patients (46 cases) with ictal MEG who underwent epilepsy surgery was included. We examined the localization of each modality, surgical resection area and seizure freedom after surgery.

RESULTS Twenty-one (45.7%) out of 46 cases were seizure-free at more than 6 months follow-up. Median duration of postoperative follow-up was 16.5 months. The patients in whom ictal, interictal single equivalent current dipole (SECD) and MRI lesion localization were completely included in the resection had a higher chance of being seizure-free significantly ($p < 0.05$).

Concordance between ictal and interictal SECD localizations was significantly associated with seizure-freedom. Concordance between MRI lesion and ictal SECD, concordance between ictal ICEEG and ictal and interictal SECD, as well as concordance between ictal ICEEG and MRI lesion were significantly associated with seizure freedom.

CONCLUSIONS Ictal MEG can contribute useful information for delineating the resection area in epilepsy surgery.

SIGNIFICANCE Resection should include ictal, interictal SECDs and MRI lesion localization, when feasible. Concordant ictal and interictal SECDs on MEG can be a favorable predictor of seizure freedom.

Keywords: Epilepsy surgery, Epileptogenic zone, Ictal magnetoencephalography, Intracranial electroencephalography, Seizure free, Seizure outcome, Stereo-electroencephalography

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2023), Vol. 145 (36443170) (1 citation)

Epilepsy highlight: Ictal MEG in epilepsy surgery candidates - Results from largest cohort (2023)

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Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2023), Vol. 145 (36435692) (0 citations)

Changes in functional connectivity in newly diagnosed self-limited epilepsy with centrotemporal spikes and cognitive impairment: An MEG study (2022)

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PURPOSE Our purpose was to explore the relationship between cognitive impairment and neural network changes in patients newly diagnosed with self-limited epilepsy with centrotemporal spikes (SeLECTS).

METHODS The Wechsler Intelligence Scale for Children, fourth edition was used to divide all SeLECTS patients into two groups: patients with full-scale intelligence quotient (FSIQ) below 80 that corresponded to cognitive impairment, and patients with FSIQ above 80 that corresponded to a normal cognitive function. The data on the resting state were recorded using magnetoencephalography. The properties of the networks were analyzed using graph theory (GT) analysis.

RESULTS The functional connectivity (FC) of the frontal cortex in patients with FSIQ < 80 was reduced in the 12-30 Hz frequency band, and the FC of the posterior cingulate cortex was reduced in the 80-250 and 250-500 Hz frequency bands. The GT analysis showed that patients in the FSIQ < 80 group had higher strength in the 8-12 and 12-30 Hz frequency bands than those in the healthy control and FSIQ > 80 group. However, the path length was reduced in the 80-250 Hz band, and the clustering coefficient was reduced in the 12-30, 80-250, and 250-500 Hz frequency bands. Moreover, the receiver operator characteristic analysis showed that the clustering coefficient in the 12-30 and 80-250 Hz frequency bands, as well as the path length in the 80-250 Hz frequency band possessed a good discriminative ability in distinguishing the FSIQ > 80 group.

CONCLUSIONS SeLECTS patients with cognitive impairment in the early stage of the disease developed disordered networks in cognitive-related brain regions. The clustering coefficient in the 12-30 and 80-250 Hz frequency bands as well as the path length in the 80-250 Hz frequency band might be good indicators to distinguish the cognitive impairment of SeLECTS patients at the early stage.

Keywords: cognitive function, functional connectivity, magnetoencephalography, multifrequency bands, self-limited epilepsy with centrotemporal spikes

Brain and behavior (2022), Vol. 12, No. 12 (36408856) (1 citation)

Network alterations in eating epilepsy during resting state and during eating using Magnetoencephalography (2022)

Gautham, Bhargava; Chatterjee, Aparajita; Kenchaiah, Raghavendra; Narayanan, Mariyappa; Duble, Shishir; Chowdary Mundlamuri, Ravindranadh; Asranna, Ajay; Bharath, Rose Dawn; Saini, Jitender; Sinha, Sanjib

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OBJECTIVE Eating epilepsy presents various imaging and electrophysiological features along with various seizure triggers. As such, network changes in eating epilepsy have not been comprehensively explored. This study was conducted to illustrate resting state network changes in eating epilepsy and to study the changes in network configurations during eating.

METHODS Magnetoencephalography recordings of nineteen patients with drug-resistant eating epilepsy were compared with healthy controls during resting state. A subgroup of nine patients and 12 controls had MEG recordings during eating. Network changes were analyzed using phase lag index across 5 frequency bands [delta, theta, alpha, beta, and gamma] using clustering coefficient (CC), betweenness centrality (BC), path length (PL), modularity (Q), and small worldness (SW).

RESULTS During the resting state, PL was decreased in patients with epilepsy in the delta, theta, and gamma band. Q was lower in patients with epilepsy in the beta and gamma bands. During eating, in patients with epilepsy, PL and SW were increased in all frequency bands, and Q was decreased in the beta band and increased in the rest of the frequency bands. Patients with mixed types of seizures showed higher PL in all bands except alpha, higher Q in all bands, and higher SW in the alpha and beta bands. Node-wise changes in CC and BC implicated changes in DMN and 'eating' networks.

CONCLUSION Reflex Eating epilepsy presents with a hyperconnected network that exacerbates during eating. The cause of seizure onset and loss of consciousness in eating epilepsy might be due to aberrant network interaction between the regions of the brain involved with eating, such as the sensorimotor cortex, lateral parietal cortex, and insula with the limbic cortex and default mode network across multiple frequency bands.

Keywords: Eating epilepsy, Graph theory, MEG, PLI

Epilepsy & behavior: E&B (2022), Vol. 137, No. Pt A (36379187) (0 citations)

Data-driven approach for the delineation of the irritative zone in epilepsy in MEG (2022)

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ABSTRACT The reliable identification of the irritative zone (IZ) is a prerequisite for the correct clinical evaluation of medically refractory patients affected by epilepsy. Given the complexity of MEG data, visual analysis of epileptiform neurophysiological activity is highly time consuming and might leave clinically relevant information undetected. We recorded and analyzed the interictal activity from seven patients affected by epilepsy (Vectorview Neuromag), who successfully underwent epilepsy surgery (Engel > = II). We visually marked and localized characteristic epileptiform activity (VIS). We implemented a two-stage pipeline for the detection of interictal spikes and the delineation of the IZ. First, we detected candidate events from peaky ICA components, and then clustered events around spatio-temporal patterns identified by convolutional sparse coding. We used the average of clustered events to create IZ maps computed at the amplitude peak (PEAK), and at the 50% of the peak ascending slope (SLOPE). We validated our approach by computing the distance of the estimated IZ (VIS, SLOPE and PEAK) from the border of the surgically resected area (RA). We identified 25 spatiotemporal patterns mimicking the underlying interictal activity (3.6 clusters/patient). Each cluster was populated on average by 22.1 [15.0-31.0] spikes. The predicted IZ maps had an average distance from the resection margin of 8.4 ± 9.3 mm for visual analysis, 12.0 ± 16.5 mm for SLOPE and 22.7 ±. 16.4 mm for PEAK. The consideration of the source spread at the ascending slope provided an IZ closer to RA and resembled the analysis of an expert observer. We validated here the performance of a data-driven approach for the automated detection of interictal spikes and delineation of the IZ. This computational framework provides the basis for reproducible and bias-free analysis of MEG recordings in epilepsy.

PloS one (2022), Vol. 17, No. 10 (36282803) (0 citations)

Virtual MEG sensors based on beamformer and independent component analysis can reconstruct epileptic activity as measured on simultaneous intracerebral recordings (2022)

Velmurugan, Jayabal; Badier, Jean-Michel; Pizzo, Francesca; Medina Villalon, Samuel; Papageorgakis, Christos; López-Madrona, Victor; Jegou, Aude; Carron, Romain; Bartolomei, Fabrice; Bénar, Christian-G

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ABSTRACT The prevailing gold standard for presurgical determination of epileptogenic brain networks is intracerebral EEG, a potent yet invasive approach. Magnetoencephalography (MEG) is a state-of-the art non-invasive method for investigating epileptiform discharges. However, it is not clear at what level the precision offered by MEG can reach that of SEEG. Here, we present a strategy for non-invasively retrieving the constituents of the interictal network, with high spatial and temporal precision. Our method is based on MEG and a combination of spatial filtering and independent component analysis (ICA). We validated this approach in twelve patients with drug-resistant focal epilepsy, thanks to the unprecedented ground truth provided by simultaneous recordings of MEG and SEEG. A minimum variance adaptive beamformer estimated the source time series and ICA was used to further decompose these time series into network constituents (MEG-ICs), each having a time series (virtual electrode) and a topography (spatial distribution of amplitudes in the brain). We show that MEG has a considerable sensitivity of 0.80 and 0.84 and a specificity of 0.93 and 0.91 for reconstructing deep and superficial sources, respectively, when compared to the ground truth (SEEG). For each epileptic MEG-IC (n = 131), we found at least one

significantly correlating SEEG contact close to zero lag after correcting for multiple comparisons. All the patients except one had at least one epileptic component that was highly correlated (Spearman rho>0.3) with that of SEEG traces. MEG-ICs correlated well with SEEG traces. The strength of correlation coefficients did not depend on the depth of the SEEG contacts or the clinical outcome of the patient. A significant proportion of the MEG-ICs (n = 83/131) were localized in proximity with their maximally correlating SEEG, within a mean distance of 20±12.18mm. Our research is the first to validate the MEG-retrieved beamformer IC sources against SEEG-derived ground truth in a simultaneous MEG-SEEG framework. Observations from the present study suggest that non-invasive MEG source components may potentially provide additional information, comparable to SEEG in a number of instances.

Keywords: Epileptogenic zone, MEG and intracranial EEG, Simultaneous MEG and SEEG, Source ICA, Virtual sensors

NeuroImage (2022), Vol. 264 (36270623) (1 citation)

Mapping Interictal activity in epilepsy using a hidden Markov model: A magnetoencephalography study (2023)

Seedat, Zelekha A; Rier, Lukas; Gascoyne, Lauren E; Cook, Harry; Woolrich, Mark W; Quinn, Andrew J; Roberts, Timothy P L; Furlong, Paul L; Armstrong, Caren; St Pier, Kelly; Mullinger, Karen J; Marsh, Eric D; Brookes, Matthew J; Gaetz, William

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ABSTRACT Epilepsy is a highly heterogeneous neurological disorder with variable etiology, manifestation, and response to treatment. It is imperative that new models of epileptiform brain activity account for this variability, to identify individual needs and allow clinicians to curate personalized care. Here, we use a hidden Markov model (HMM) to create a unique statistical model of interictal brain activity for 10 pediatric patients. We use magnetoencephalography (MEG) data acquired as part of standard clinical care for patients at the Children's Hospital of Philadelphia. These data are routinely analyzed using excess kurtosis mapping (EKM); however, as cases become more complex (extreme multifocal and/or polymorphic activity), they become harder to interpret with EKM. We assessed the performance of the HMM against EKM for three patient groups, with increasingly complicated presentation. The difference in localization of epileptogenic foci for the two methods was 7 ± 2 mm (mean ± SD over all 10 patients); and 94% ± 13% of EKM temporal markers were matched by an HMM state visit. The HMM localizes epileptogenic areas (in agreement with EKM) and provides additional information about the relationship between those areas. A key advantage over current methods is that the HMM is a data-driven model, so the output is tuned to each individual. Finally, the model output is intuitive, allowing a user (clinician) to review the result and manually select the HMM epileptiform state, offering multiple advantages over previous methods and allowing for broader implementation of MEG epileptiform analysis in surgical decision-making for patients with intractable epilepsy.

Keywords: epilepsy, hidden Markov model, interictal activity, magnetoencephalography

Human brain mapping (2023), Vol. 44, No. 1 (36259549) (1 citation)

EMHapp: a pipeline for the automatic detection, localization and visualization of epileptic magnetoencephalographic high-frequency oscillations (2022)

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ABSTRACT Objective.High-frequency oscillations (HFOs) are promising biomarkers for localizing epileptogenic brain tissue. Previous studies have revealed that HFOs that present concurrence with interictal epileptic discharges (IEDs) better delineate epileptogenic brain tissue, particularly for epilepsy patients with multitype interictal discharges. However, the analysis of noninvasively recorded epileptic HFOs involves many complex procedures, such as data preprocessing, detection and source localization, impeding the translation of this approach to clinical practice.Approach. To address these problems, we developed a graphical user interface (GUI)-based pipeline called EMHapp, which can be used for the automatic detection, source localization and visualization of HFO events concurring with IEDs in magnetoencephalography (MEG) signals by using a beamformer-based virtual sensor (VS) technique. An improved VS reconstruction method was developed to enhance the amplitudes of both HFO and IED VS signals. To test the capability of our pipeline, we collected MEG data from 11 complex focal epilepsy patients with surgical resections or seizure onset zones (SOZs) that were identified by intracranial electroencephalography.Main results.Our results showed that the HFO sources of eight patients were concordant with their resection margins or SOZs. Our proposed VS signal reconstruction approach achieved an 83.2% improvement regarding the number of detected HFO events and a 17.3% improvement in terms of the spatial overlaps between the HFO sources and the resection margins or SOZs in comparison with conventional VS reconstruction approaches.Significance.EMHapp is the first GUI-based pipeline for the analysis of epileptic magnetoencephalographic HFOs, which conveniently obtains HFO source locations using clinical data and enables direct translation to clinical applications.

Keywords: MEG, beamformer, epilepsy, high-frequency oscillations, interictal epileptic discharges

Journal of neural engineering (2022), Vol. 19, No. 5 (36108595) (0 citations)

The long-term surgical outcomes of low-grade epilepsy-associated neuroepithelial tumors (2022)

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OBJECTIVE This study aimed to evaluate the surgical outcomes and relevant prognostic factors in patients with low-grade epilepsy-associated neuroepithelial tumors (LEAT) and, especially, to develop a scoring system to predict postoperative seizure outcomes.

METHODS The clinical data of patients who underwent epilepsy surgery for LEAT were retrospectively studied. The surgical outcomes of seizure and neurological statuses in patients were evaluated using Engel classification and modified Rankin Scale (mRS) scoring, respectively. A scoring system of seizure outcomes was constructed based on the weight of the β-coefficient estimate of each predictor in the final multivariate predicting model of seizure outcomes.

RESULTS Of the 287 patients (106 female) enrolled, the median age was 19 years at surgery and 10 years at seizure onset, with a median duration of epilepsy of

60 months. Among 258 patients who were followed up for at least 12 months, 215 (83.3%) patients had a favorable seizure outcome (Engel class I) after surgery, and 43 (16.7%) patients had an unfavorable seizure outcome; longer duration of epilepsy, discordant magnetoencephalography (MEG) findings, and acute postoperative seizures were significantly included in the scoring system to predict unfavorable seizure outcomes, and in the scoring system, accumulated scoring of 0-19 scores was recorded, which were finally grouped into three risk levels: low risk (risk < 30%), medium risk (30% ≤ risk < 70%), and high risk (risk ≥ 70%). In addition, favorable neurological outcomes (mRS score 0-1) were recorded in 187 (72.5%) patients, while unfavorable neurological outcomes were recorded in 71 (27.5%) patients, which were significantly related to poor seizure control, older age at surgery, and longer duration of epilepsy and hospitalization time.

SIGNIFICANCE The long-term surgical outcomes of LEAT after surgery were satisfactory. A scoring system for predicting unfavorable seizure outcomes with different risk levels was developed, which could partly guide clinical treatments of LEAT.

Keywords: brain tumor, epilepsy surgery, neurological outcome, prognostic factor, seizure outcome

Epilepsia open (2022), Vol. 7, No. 4 (36081402) (1 citation)

Clinical validation of magnetoencephalography network analysis for presurgical epilepsy evaluation (2022)

Fujiwara, Hisako; Kadis, Darren S; Greiner, Hansel M; Holland, Katherine D; Arya, Ravindra; Aungaroon, Gewalin; Fong, Susan L; Arthur, Todd M; Kremer, Kelly M; Lin, Nan; Liu, Wei; Mangano, Francesco T; Skoch, Jesse; Horn, Paul S; Tenney, Jeffrey R

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OBJECTIVE To clinically validate the connectivity-based magnetoencephalography (MEG) analyses to identify seizure onset zone (SOZ) with comparing to equivalent current dipole (ECD).

METHODS The ECD cluster was quantitatively analyzed by calculating the centroid of the cluster and maximum distance (the largest distance between all dipoles). The "primary hub" was determined by the highest eigencentrality. The distribution of nodes in the top 5% of eigenvector centrality values was quantified by generating the convex hull between each node.

RESULTS Thirty-one patients who underwent MEG, stereotactic-EEG, and focal surgery were included. The primary hub was significantly closer to the sEEG-defined SOZ compared to ECD ($p = 0.009$). The seizure freedom positive and negative predictive values of complete ECD cluster and primary hub resections did not significantly differ, although complete resection of the primary hub showed slightly better negative predictive value (ECD: 50.0% NPV, hub: 64.7% NPV). Both quantitative ECD and functional connectivity analyses suggested that spatially restricted dipole distributions and higher connectivity in a smaller region correlate with better seizure outcomes.

CONCLUSIONS Our findings suggest that MEG network analysis could be a valuable complement to the ECD methods.

SIGNIFICANCE The results of this study are an important step towards using non-invasive neurophysiologic recordings to accurately define the epileptic network.

Keywords: Drug-resistant epilepsy, Eigenvector centrality, Functional connectivity, Magnetoencephalography, Surgical outcome

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2022), Vol. 142 (36063669) (1 citation)

Immediate Effects of Vagal Nerve Stimulation in Drug-Resistant Epilepsy Revealed by Magnetoencephalographic Recordings (2023)

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ABSTRACT Objective: Vagus nerve stimulation (VNS) has been a neuromodulatory option for treating drug-resistant epilepsy (DRE), but its mechanism remains unclear. To obtain insight into the mechanism by which VNS reduces epileptic seizures, the immediate effects of VNS in brain networks of DRE patients were investigated when the patients' vagal nerve stimulators were turned on. Methods: The brain network properties of 14 DRE patients with a vagal nerve stimulator and 14 healthy controls were evaluated using magnetoencephalography recordings for 6 main frequency bands. Results: Compared with healthy controls, DRE patients exhibited significant increases in functional connectivity in the theta, alpha, beta, and gamma bands and significant reductions in the small-world measure in the theta and beta bands. During periods when patients' vagal nerve stimulators were turned on, DRE patients showed significant reductions in functional connectivity in the theta and alpha bands and a significant increase in the small-world measure in the theta band when compared with periods when patients' vagal nerve stimulators were turned off. Conclusions: Our results indicate that the brain networks of DRE patients were pathologically hypersynchronous and instantaneous VNS can decrease the synchronization of brain networks of epileptic patients, which might play a key role in the mechanism by which VNS reduces epileptic seizures. In the theta band, instantaneous VNS can increase the network efficiency of DRE patients, and the increment in network efficiency may be helpful for improving brain cognitive function in epileptic patients. Impact statement For the first time, we investigated the immediate effects of vagus nerve stimulation (VNS) in the brain networks of drug-resistant epilepsy patients using magnetoencephalography. Our results show that instantaneous VNS can decrease the hypersynchronization of epileptic networks and increase the network efficiency of epileptic patients. Our results are helpful in understanding the mechanism of action by which VNS reduces epileptic seizures and improves the cognitive function in epileptic patients and the brain network reorganization caused by long-term VNS.

Keywords: brain networks, drug-resistant epilepsy, functional connectivity, graph theory, magnetoencephalography, vagal nerve stimulation

Brain connectivity (2023), Vol. 13, No. 1 (35974665) (0 citations)

Child Neurology: Functional Evaluation of the Dominant Hemisphere Using Magnetoencephalography Prior to Hemispherectomy (2022)

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ABSTRACT Rasmussen encephalitis is a devastating progressive inflammatory disorder that leads to debilitating neurologic deficits and intractable epilepsy. Surgical treatment of the dominant hemisphere has been attempted with hesitation, given the lack of effective diagnostic tools to determine the potential functional deficits from disconnection procedures.

Neurology (2022), Vol. 99, No. 14 (35918155) (0 citations)

Feasibility of Tailored Unilateral Disconnection vs Callosotomy for Refractory Epilepsy in Patients with Bilateral Parieto-Occipital Gliosis Following Perinatal Insult (2022)

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BACKGROUND Patients with perinatal hypoxia (PH) and drug-refractory epilepsy (DRE) often have bilateral parieto-occipital gliosis. Surgical management of such patients is a dilemma.

OBJECTIVE To identify preoperative determinants for unilateral disconnection vs callosotomy, and analyze the surgical outcome in such patients.

METHODS AND MATERIAL This was a retrospective analysis of patients with DRE and history of PH, with MRI abnormalities restricted to bilateral posterior quadrants. Preoperative semiology, epilepsy duration and seizure frequency were recorded. Based on the concordance between the results of non-invasive tests, patients underwent either posterior quadrant disconnection (PQD) or corpus callosotomy (CC). Preoperative variables were analyzed and corelated to the postoperative seizure freedom.

RESULTS Fourteen patients were identified, 6 underwent PQD and 8 underwent CC. At follow up of 39.17 ± 23.75 months, 66.66% of patients (4/6) in the PQD subgroup had an ILAE Class I outcome. While none in the CC group attained seizure freedom, 87.5% (7/8) had more than 50% reduction in seizure frequency (follow up: 42 ± 27.31 months). Patients with a poor outcome had significantly greater seizure frequency (P = 0.05) and history of drop attacks (P = 0.04) in both the groups. Magnetoencephalography (MEG) accurately localized the epileptogenic zone in all of the patients with good outcome (P = 0.015). Concordance with single photon emission tomography (SPECT) was also a predictor of favorable outcome (P = 0.041).

CONCLUSIONS A history of drop attacks with high seizure frequency is associated with poor postoperative seizure outcome. Unilateral PQD is feasible and leads to superior seizure-free outcomes, even in cases with widespread and bilateral imaging and electrical abnormalities, provided the other preoperative investigations are concordant in localizing the epileptogenic zone.

Keywords: Drug refractory epilepsy, hypoxic ischemic encephalopathy, pediatric epilepsy, perinatal hypoxia, posterior quadrant disconnection

Neurology India (2022), Vol. 70, No. 3 (35864619) (0 citations)

Characterization of cortical activity in juvenile myoclonic epilepsy by gradient magnetic field topography (2022)

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OBJECTIVE Gradient magnetic field topography (GMFT) illustrates the magnetic field gradients of epileptic spike or polyspikes (S/PS) activities on a volume-rendered brain surface. The purpose is to characterize cortical activation in juvenile myoclonic epilepsy (JME).

METHODS We compared interictal S/PS activities in 10 patients with JME to five patients with Lennox-Gastaut syndrome (LGS). We defined areas with gradients exceeding 300fT/cm as activated zones (AZs) on GMFT. We defined the hemisphere where an AZ initially appeared as the "preceding hemisphere". We localized the foci where AZs arose and evaluated their spatiotemporal changes.

RESULTS In JME, the localization of S/PS in the preceding hemisphere was frontal in 18 activities (28%), parietal in 10 (15%), and frontal/parietal in 33 (51%), and in the contralateral hemisphere it was frontal in 14 (32%), parietal in 6 (14%), and frontal/parietal in 19 (43%). In LGS, AZs arose in every lobe of the brain. The median interhemispheric time difference was 7 ms (range: 0-20) in JME, which was significantly shorter than the 19 ms (1-50) observed among patients with LGS ($p < 0.0001$).

CONCLUSIONS AZs are localized within the bilateral frontal and parietal regions. AZs arose serially from foci with small time differences.

SIGNIFICANCE These results are consistent with regional network involvement in JME.

Keywords: Gradient magnetic field topography, Juvenile myoclonic epilepsy, Magnetoencephalography, Regional network involvement, Working memory network

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2022), Vol. 141 (35853311) (1 citation)

Wearable OPM-MEG: A changing landscape for epilepsy (2022)

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ABSTRACT Magnetoencephalography with optically pumped magnometers (OPM-MEG) is an emerging and novel, cost-effective wearable system that can simultaneously record neuronal activity with high temporal resolution ("when" neuronal activity occurs) and spatial resolution ("where" neuronal activity occurs). This paper will first outline recent methodological advances in OPM-MEG compared to conventional superconducting quantum interference device (SQUID)-MEG before discussing how OPM-MEG can become a valuable and noninvasive clinical support tool in epilepsy surgery evaluation. Although OPM-MEG and SQUID-MEG share similar data features, OPM-MEG is a wearable design that fits children and adults, and it is also robust to head motion within a magnetically shielded room. This means that OPM-MEG can potentially extend the application of MEG into the neurobiology of severe childhood epilepsies with intellectual disabilities (e.g., epileptic encephalopathies) without sedation. It is worth noting that most OPM-MEG sensors are heated, which may become an issue with large OPM sensor arrays (OPM-MEG currently has fewer sensors than SQUID-MEG). Future implementation of triaxial sensors may alleviate the need for large OPM sensor arrays. OPM-MEG designs allowing both awake and sleep recording are essential for potential long-term epilepsy monitoring.

Keywords: EEG, MEG, MRI, OPM-MEG, brain surgery, epilepsy

Epilepsia (2022), Vol. 63, No. 11 (35841260) (2 citations)

Prognostic value of high-frequency oscillations combined with multimodal imaging methods for epilepsy surgery (2022)

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BACKGROUND The combination of high-frequency oscillations (HFOs) with single-mode imaging methods has been proved useful in identifying epileptogenic zones, whereas few studies have examined HFOs combined with multimodal imaging methods. The aim of this study was to evaluate the prognostic value of ripples, an HFO subtype with a frequency of 80 to 200Hz is combined with multimodal imaging methods in predicting epilepsy surgery outcome.

METHODS HFOs were analyzed in 21 consecutive medically refractory epilepsy patients who underwent epilepsy surgery. All patients underwent positron emission tomography (PET) and deep electrode implantation for stereo-electroencephalography (SEEG); 11 patients underwent magnetoencephalography (MEG). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in predicting surgical outcome were calculated for ripples combined with PET, MEG, both PET and MEG, and PET combined with MEG. Kaplan-Meier survival analyses were conducted in each group to estimate prognostic value.

RESULTS The study included 13 men and 8 women. Accuracy for ripples, PET, and MEG alone in predicting surgical outcome was 42.9%, 42.9%, and 81.8%, respectively. Accuracy for ripples combined with PET and MEG was the highest. Resection of regions identified by ripples, MEG dipoles, and combined PET findings was significantly associated with better surgical outcome ($P < 0.05$).

CONCLUSIONS Intracranial electrodes are essential to detect regions which generate ripples and to remove these areas which indicate good surgical outcome for medically intractable epilepsy. With the assistance of presurgical noninvasive imaging examinations, PET and MEG, for example, the SEEG electrodes would identify epileptogenic regions more effectively.

Chinese medical journal (2022), Vol. 135, No. 9 (35773966) (0 citations)

Retrospective comparison of motor and somatosensory MEG mapping-Considerations for better clinical applications (2022)

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ABSTRACT While magnetoencephalography (MEG) has proven to be a valuable and reliable tool for presurgical functional mapping of eloquent cortices for at least two decades, widespread use of this technique by clinicians has remained elusive. This modest application may be attributable, at least in part, to misunderstandings regarding the success rate of such mapping procedures, as well as the primary sources contributing to mapping failures. To address this, we conducted a retrospective comparison of sensorimotor functional mapping success rates in 141 patients with epilepsy and 75 tumor patients from the Center for MEG in Omaha, NE. Neurosurgical candidates either completed motor mapping (i.e., finger tapping paradigm), somatosensory mapping (i.e., peripheral stimulation paradigm), or both motor and somatosensory protocols during MEG. All MEG data underwent subsequent time-domain averaging and source localization of left and right primary motor (M1) and somatosensory (S1) cortices was conducted using a single equivalent dipole model. Successful mapping was determined based on dipole goodness of fit metrics 95%, as well as an accurate and conceivable spatial correspondence to precentral and postcentral gyri for M1 and S1, respectively. Our results suggest that mapping M1 in epilepsy and tumor patients was on average 94.5% successful, when patients only completed motor mapping protocols. In contrast, mapping S1 was successful 45-100% of the time in these patient groups when they only completed somatosensory mapping paradigms. Importantly, Z-tests for independent proportions revealed that the percentage of successful S1 mappings significantly increased to 94% in epilepsy patients who completed both motor/somatosensory mapping protocols during MEG. Together, these data suggest that ordering more comprehensive mapping procedures (e.g., both motor and somatosensory protocols for a collective sensorimotor network) may substantially increase the accuracy of presurgical functional mapping by providing more extensive data from which to base interpretations. Moreover, clinicians and magnetoencephalographers should be considerate of the major contributors to mapping failures (i.e., low SNR, excessive motion and magnetic artifacts) in order to further increase the percentage of cases achieving successful mapping of eloquent cortices.

Keywords: Epilepsy, Magnetoencephalography, Postcentral gyrus, Precentral gyrus, Presurgical mapping, Tumor

NeuroImage. Clinical (2022), Vol. 35 (35597033) (1 citation)

Fully-Automated Spike Detection and Dipole Analysis of Epileptic MEG Using Deep Learning (2022)

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ABSTRACT Magnetoencephalography (MEG) is a useful tool for clinically evaluating the localization of interictal spikes. Neurophysiologists visually identify spikes from the MEG waveforms and estimate the equivalent current dipoles (ECD). However, presently, these analyses are manually performed by neurophysiologists and are time-consuming. Another problem is that spike identification from MEG waveforms largely depends on neurophysiologists' skills and experiences. These problems cause poor cost-effectiveness in clinical MEG examination. To overcome these problems, we fully automated spike identification and ECD estimation using a deep learning approach fully automated AI-based MEG interictal epileptiform discharge identification and ECD estimation (FAMED). We applied a semantic segmentation method, which is an image processing technique, to identify the appropriate times between spike onset and peak and to select appropriate sensors for ECD estimation. FAMED was trained and evaluated using clinical MEG data acquired from 375 patients. FAMED training was performed in two stages: in the first stage, a classification network was learned, and in the second stage, a segmentation network that extended the classification network was learned. The classification network had a mean AUC of 0.9868 (10-fold patient-wise cross-validation); the sensitivity and specificity were 0.7952 and 0.9971, respectively. The median distance between the ECDs estimated by the neurophysiologists and those using FAMED was 0.63 cm. Thus, the performance of FAMED is comparable to that of neurophysiologists, and it can contribute to the efficiency and consistency of MEG ECD analysis.

IEEE transactions on medical imaging (2022), Vol. 41, No. 10 (35536808) (2 citations)

Classification of EEG Signal-Based Encephalon Magnetic Signs for Identification of Epilepsy-Based Neurological Disorder (2022)

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ABSTRACT Magnetoencephalography (MEG) is now widely used in clinical examinations and medical research in many fields. Resting-state magnetoencephalography-based brain network analysis can be used to study the physiological or pathological mechanisms of the brain. Furthermore, magnetoencephalography analysis has a significant reference value for the diagnosis of epilepsy. The scope of the proposed research is that this research demonstrates how to locate spikes in the phase locking functional brain connectivity network of the Desikan-Killiany brain region division using a neural network approach. It also improves detection accuracy and reduces missed and false detection rates. The automatic classification of epilepsy encephalomagnetic signals can make timely judgments on the patient's condition, which is of tremendous clinical significance. The existing literature's research on the automatic type of epilepsy EEG signals is relatively sufficient, but the research on epilepsy EEG signals is relatively weak. A full-band machine learning automatic discrimination method of epilepsy brain magnetic spikes based on the brain functional connection network is proposed. The four classifiers are comprehensively compared. The classifier with the best effect is selected, and the discrimination accuracy can reach 93.8%. Therefore, this method has a good application prospect in automatically identifying and labeling epileptic spikes in magnetoencephalography.

Computational and mathematical methods in medicine (2022), Vol. 2022 (35529257) (0 citations)

On-Scalp Optically Pumped Magnetometers versus Cryogenic Magnetoencephalography for Diagnostic Evaluation of Epilepsy in School-aged Children (2022)

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ABSTRACT Background Magnetoencephalography (MEG) is an established method used to detect and localize focal interictal epileptiform discharges (IEDs). Current MEG systems house hundreds of cryogenic sensors in a rigid, one-size-fits-all helmet, which results in several limitations, particularly in children. Purpose To determine if on-scalp MEG based on optically pumped magnetometers (OPMs) alleviates the main limitations of cryogenic MEG. Materials and Methods In this prospective single-center study conducted in a tertiary university teaching hospital, participants underwent cryogenic (102 magnetometers, 204 planar gradiometers) and on-scalp (32 OPMs) MEG. The two modalities for the detection and localization of IEDs were compared. The t test was used to compare IED amplitude and signal-to-noise ratio (SNR). Distributed source modeling was performed on OPM-based and cryogenic MEG data. Results Five children (median age, 9.4 years [range, 5-11 years]; four girls) with self-limited idiopathic (n = 3) or refractory (n = 2) focal epilepsy were included. IEDs were identified in all five children with comparable sensor topographies for both MEG devices. IED amplitudes were 2.3 (7.2 of 3.1) to 4.6 (3.2

of 0.7) times higher (P < .001) with on-scalp MEG, and the SNR was 27% (16.7 of 13.2) to 60% (12.8 of 8.0) higher (P value range: .001-.009) with on-scalp MEG in all but one participant (P = .93), whose head movements created pronounced motion artifacts. The neural source of averaged IEDs was located at approximately 5 mm (n = 3) or higher (8.3 mm, n = 1; 15.6 mm, n = 1) between on-scalp and cryogenic MEG. Conclusion Despite the limited number of sensors and scalp coverage, on-scalp magnetoencephalography (MEG) based on optically pumped magnetometers helped detect interictal epileptiform discharges in school-aged children with epilepsy with a higher amplitude, higher signal-to-noise ratio, and similar localization value compared with conventional cryogenic MEG. Online supplemental material is available for this article. © RSNA, 2022 See also the editorial by Widjaja in this issue.

Radiology (2022), Vol. 304, No. 2 (35503013) (7 citations)

Magnetoencephalography in clinical practice (2022)

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ABSTRACT Magnetoencephalography (MEG) is a neurophysiological technique that measures the magnetic fields associated with neuronal activity in the brain. It is closely related but distinct from its counterpart electroencephalography (EEG). The first MEG was recorded more than 50 years ago and has technologically evolved over this time. It is now well established in clinical practice particularly in the field of epilepsy surgery and functional brain mapping. However, underutilization and misunderstanding of the clinical applications of MEG is a challenge to more widespread use of this technology. A fundamental understanding of the neurophysiology and physics of MEG is discussed in this article as well as practical issues related to implementation, analysis, and clinical applications. The future of MEG and some potential clinical applications are briefly reviewed.

Arquivos de neuro-psiquiatria (2022), Vol. 80, No. 5 (35486819) (0 citations)

Fast parametric curve matching (FPCM) for automatic spike detection (2022)

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ABSTRACT Objective. Epilepsy is a widely spread neurological disease, whose treatment often requires resection of the pathological cortical tissue. Interictal spike analysis observed in the non-invasively collected EEG or MEG data offers an attractive way to localize epileptogenic cortical structures for surgery planning purposes. Interictal spike detection in lengthy multichannel data is a daunting task that is still often performed manually. This frequently limits such an analysis to a small portion of the data which renders the appropriate risks of missing the potentially epileptogenic region. While a plethora of automatic spike detection techniques have been developed each with its own assumptions and limitations, none of them is ideal and the best results are achieved when the output of several automatic spike detectors are combined. This is especially true in the low signal-to-noise ratio conditions. To this end we propose a novel biomimetic approach for automatic spike detection based on a constrained mixed spline machinery that we dub as fast parametric curve matching (FPCM).Approach. Using the peak-wave shape parametrization, the constrained parametric morphological model is constructed and convolved with the observed multichannel data to efficiently determine mixed spline parameters corresponding to each time-point in the dataset. Then the logical predicates that directly map to verbalized textbook like descriptions of the expected interictal event morphology allow us to accomplish the spike detection task.Main results. The results of simulations mimicking typical low SNR scenarios show the robustness and high receiver operating characteristic AUC values of the FPCM method as compared to the spike detection performed using more conventional approaches such as wavelet decomposition, template matching or simple amplitude thresholding. Applied to the real MEG and EEG data from the human patients and to rat ECoG data, the FPCM technique demonstrates reliable detection of the interictal events and localization of epileptogenic zones concordant with independent conclusions made by the epileptologist.Significance. Since the FPCM is computationally light, tolerant to high amplitude artifacts and flexible to accommodate verbalized descriptions of an arbitrary target morphology, it is likely to complement the existing arsenal of means for analysis of noisy interictal datasets.

Keywords: EEG, MEG, automatic detection, epilepsy, interictal spikes

Journal of neural engineering (2022), Vol. 19, No. 3 (35439749) (0 citations)

Repetitive transcranial magnetic stimulation to treat benign epilepsy with centrotemporal spikes (2022)

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OBJECTIVES To investigate the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) on patients with benign epilepsy with centrotemporal spikes (BECTS).

METHODS In this open pilot study, we enrolled four BECTS patients who had frequent seizures (at least 3 seizures during the 3-month baseline). After localizing sources of interictal epileptiform discharges (IEDs) with magnetoencephalography, IEDs-source-rTMS (1 Hz) with 500 pulses at 90% of resting motor threshold was applied for 10 weekdays in each patient. The primary outcome measure was the seizure-reduction rate after rTMS. Other outcome measures were the spike-wave index (SWI), behavioral evaluation, and adverse effects.

RESULTS All four patients received at least 3 months seizure-free after rTMS. Compared with baseline, SWI decreased significantly after rTMS in three patients (patient 1, 3 and 4) ($P = .002$, $P = .007$, and $P < .001$, respectively). Attention deficit identified in two patients in baseline recovered to the normal range after rTMS. No adverse effect was observed.

DISCUSSION Our preliminary observation provides a promising approach to reducing clinical seizures for BECTS with frequent seizures. Of importance, our data may provide a potentially novel method for the high prevalence of behavioral problems in BECTS patients via decreasing cortical hyperexcitability.

Keywords: Benign epilepsy with centrotemporal spikes, Electroencephalogram, Epilepsy, Neuromodulation, Repetitive transcranial magnetic stimulation

Brain stimulation (2022), Vol. 15, No. 3 (35427811) (1 citation)

Combined electrophysiological and morphological phenotypes in patients with genetic generalized epilepsy and their healthy siblings (2022)

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OBJECTIVE Genetic generalized epilepsy (GGE) is characterized by aberrant neuronal dynamics and subtle structural alterations. We evaluated whether a combination of magnetic and electrical neuronal signals and cortical thickness would provide complementary information about network pathology in GGE. We also investigated whether these imaging phenotypes were present in healthy siblings of the patients to test for genetic influence.

METHODS In this cross-sectional study, we analyzed 5 min of resting state data acquired using electroencephalography (EEG) and magnetoencephalography (MEG) in patients, their siblings, and controls, matched for age and sex. We computed source-reconstructed power and connectivity in six frequency bands (1-40 Hz) and cortical thickness (derived from magnetic resonance imaging). Group differences were assessed using permutation analysis of linear models for each modality separately and jointly for all modalities using a nonparametric combination.

RESULTS Patients with GGE (n = 23) had higher power than controls (n = 35) in all frequencies, with a more posterior focus in MEG than EEG. Connectivity was also increased, particularly in frontotemporal and central regions in theta (strongest in EEG) and low beta frequencies (strongest in MEG), which was eminent in the joint EEG/MEG analysis. EEG showed weaker connectivity differences in higher frequencies, possibly related to drug effects. The inclusion of cortical thickness reinforced group differences in connectivity and power. Siblings (n = 18) had functional and structural patterns intermediate between those of patients and controls.

SIGNIFICANCE EEG detected increased connectivity and power in GGE similar to MEG, but with different spectral sensitivity, highlighting the importance of theta and beta oscillations. Cortical thickness reductions in GGE corresponded to functional imaging patterns. Our multimodal approach extends the understanding of the resting state in GGE and points to genetic underpinnings of the imaging markers studied, providing new insights into the causes and consequences of epilepsy.

Keywords: cortical thickness, endophenotypes, interictal, oscillations, resting state

Epilepsia (2022), Vol. 63, No. 7 (35416282) (1 citation)

Connectomic Profiles and Cognitive Trajectories After Epilepsy Surgery in Children (2022)

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BACKGROUND AND OBJECTIVES Neurocognitive outcomes after surgery for temporal lobe epilepsy in childhood are variable. Postoperative changes are not directly predicted by seizure freedom, and associations between epilepsy, neuropsychological function, and developing neural networks are poorly understood. Here, we leveraged whole-brain connectomic profiling in magnetoencephalography (MEG) to retrospectively study associations between brain connectivity and neuropsychological function in children with temporal lobe epilepsy undergoing resective surgery.

METHODS Clinical and MEG data were retrospectively analyzed for children who underwent temporal lobe epilepsy surgery at the Hospital for Sick Children from 2000 to 2021. Resting-state connectomes were constructed from neuromagnetic oscillations via the weighted-phase lag index. Using a partial least-squares (PLS) approach, we assessed multidimensional associations between patient connectomes, neuropsychological scores, and clinical covariates. Bootstrap resampling statistics were performed to assess statistical significance.

RESULTS A total of 133 medical records were reviewed, and 5 PLS analyses were performed. Each PLS analysis probed a particular neuropsychological domain and the associations between its baseline and postoperative scores and the connectomic data. In each PLS analysis, a significant latent variable was identified, representing a specific percentage of the variance in the data and relating neural networks to clinical covariates, which included changes in rote verbal memory ($n = 41$, $p = 0.01$, $\sigma[2] = 0.38$), narrative/verbal memory ($n = 57$, $p = 0.00$, $\sigma[2] = 0.52$), visual memory ($n = 51$, $p = 0.00$, $\sigma[2] = 0.43$), working memory ($n = 44$, $p = 0.00$, $\sigma[2] = 0.52$), and overall intellectual function ($n = 59$, $p = 0.00$, $\sigma[2] = 0.55$). Children with more diffuse, bilateral intrinsic connectivity across several frequency bands showed lower scores on all neuropsychological assessments but demonstrated a greater propensity for gains after resective surgery.

DISCUSSION Here, we report that connectomes characterized by diffuse connectivity, reminiscent of developmentally immature networks, are associated with lower preoperative cognition and postoperative cognitive improvement. These findings provide a potential means to understand neurocognitive function in children with temporal lobe epilepsy and expected changes postoperatively.

Neurology (2022), Vol. 98, No. 22 (35410904) (0 citations)

Utility of magnetoencephalography combined with stereo-electroencephalography in resective epilepsy surgery: A 2-year follow-up (2022)

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PURPOSE Precise and accurate implantation of stereo-electroencephalography (SEEG) electrodes is critical for the localization of the seizure onset zone (SOZ), which plays a leading role in the prognosis of resective epilepsy surgery. Magnetoencephalography (MEG) is a noninvasive technique which can delineate the epilepsy focus by visualizing interictal spikes into dipole

clusters. MEG may provide supporting information for guiding SEEG electrode implantation and improve the long-term outcomes of epilepsy surgery. In this study, we evaluated the accuracy of MEG in determining the SOZ.

METHODS We retrospectively analyzed patients with refractory epilepsy who underwent MEG examination and SEEG implantation before resective epilepsy surgery in the Shanghai Ruijin Hospital. The SEEG plan was designed according to the dipole clusters and the resections were operated according to the SEEG recordings. We investigated the relationships of the pattern of MEG dipole clusters and SEEG sampling to the final resective surgery prognosis.

RESULTS We included 42 patients with a postoperative follow-up of at least 2 years (mean 34.1 months). Eighteen (42%) patients who showed concordant localization between MEG and SEEG evaluation had a higher probability of seizure-free outcome ($p=0.046$, $\chi[2]=4.835$, odds ratio=5.00, 95% CI=1.12-22.30). Complete sampling of MEG dipole clusters by SEEG electrodes was found in 23 (54%) patients, who had higher probability of seizure-free outcome that those with incomplete sampling ($p<0.001$, odds ratio=16.67, 95% CI=3.11-89.28). MEG results showing a single, tight cluster or stable orientation were associated to better seizure outcomes after resective surgery.

CONCLUSION MEG dipole cluster helps SEEG implantation in localizing the SOZ for better long-term epilepsy surgery outcome. The MEG results can play a role as prognostic predictors of epilepsy surgery.

Keywords: Engel classification, Epilepsy surgery, Magnetoencephalography (MEG), Seizure onset zone, Stereo-electroencephalography (SEEG)

Seizure (2022), Vol. 97 (35390641) (0 citations)

Abnormal phase-amplitude coupling characterizes the interictal state in epilepsy (2022)

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ABSTRACT Objective.Diagnosing epilepsy still requires visual interpretation of electroencephalography (EEG) and magnetoencephalography (MEG) by specialists, which prevents quantification and standardization of diagnosis. Previous studies proposed automated diagnosis by combining various features from EEG and MEG, such as relative power (Power) and functional connectivity (FC). However, the usefulness of interictal phase-amplitude coupling (PAC) in diagnosing epilepsy is still unknown. We hypothesized that resting-state PAC would be different for patients with epilepsy in the interictal state and for healthy participants such that it would improve discrimination between the groups.Approach.We obtained resting-state MEG and magnetic resonance imaging (MRI) in 90 patients with epilepsy during their preoperative evaluation and in 90 healthy participants. We used the cortical currents estimated from MEG and MRI to calculate Power in theδ(1-3 Hz),θ(4-7 Hz),α(8-13 Hz),β(13-30 Hz), lowγ(35-55 Hz), and highγ(65-90 Hz) bands and FC in theθband. PAC was evaluated using the synchronization index (SI) for eight frequency band pairs: the phases ofδ, θ, α, and$\beta$and the amplitudes of low and highγ. First, we compared the mean SI values for the patients with epilepsy and the healthy participants. Then, using features such as PAC, Power, FC, and features extracted by deep learning (DL) individually or combined, we tested whether PAC improves discrimination accuracy for the two groups.Main results.The mean SI values were significantly different for the patients with epilepsy and the healthy participants. The SI value difference was highest forθ/lowγin the temporal lobe. Discrimination accuracy was the highest, at 90%, using the combination of PAC and DL.Significance.Abnormal PAC characterized the patients with epilepsy in the interictal state

compared with the healthy participants, potentially improving the discrimination of epilepsy.

Keywords: autodiagnosis, deep learning, epilepsy, magnetoencephalography, phase–amplitude coupling

Journal of neural engineering (2022), Vol. 19, No. 2 (35385832) (1 citation)

Prediction of seizure outcome following temporal lobectomy: A magnetoencephalography-based graph theory approach" (2022)

Mukherjee, Joydeep; Kenchaiah, Raghavendra; Gautham, Bhargava K; Narayanan, Chitra; Afsar, Mohammed; Narayanan, Mariyappa; Rajeswaran, Jamuna; Asranna, Ajay; Mundlamuri, Ravindranadh C; Viswanathan, Lakshminarayanapuram G; Mahadevan, Anita; Sadashiva, Nishanth; Arivazhagan, A; Karthik, K; Bharath, Rose D; Saini, Jitendra; Kandavel, Thennarasu; Rao, Malla Bhaskara; Sinha, Sanjib

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Seizure (2022), Vol. 97 (35344920) (0 citations)

Informed MEG/EEG source imaging reveals the locations of interictal spikes missed by SEEG (2022)

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ABSTRACT Determining the accurate locations of interictal spikes has been fundamental in the presurgical evaluation of epilepsy surgery. Stereo-electroencephalography (SEEG) is able to directly record cortical activity and localize interictal spikes. However, the main caveat of SEEG techniques is that they have limited spatial sampling (covering <5% of the whole brain), which may lead to missed spikes originating from brain regions that were not covered by SEEG. To address this problem, we propose a SEEG-informed minimum-norm estimates (SIMNE) method by combining SEEG with magnetoencephalography (MEG) or EEG. Specifically, the spike locations determined by SEEG offer as a priori information to guide MEG source reconstruction. Both computer simulations and experiments using data from five epilepsy patients were conducted to evaluate the performance of SIMNE. Our results demonstrate that SIMNE generates more accurate source estimation than a traditional minimum-norm estimates method and reveals the locations of spikes missed by SEEG, which would improve presurgical evaluation of the epileptogenic zone.

Keywords: Interictal spike, Inverse problem, Magnetoencephalography, Missing problem, Stereo-electroencephalography

NeuroImage (2022), Vol. 254 (35337964) (0 citations)

Utility of Functional MRI and Magnetoencephalography in the Diagnosis of Infantile Spasms and Hypsarrhythmia (2022)

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ABSTRACT Neuroimaging and neurophysiology techniques can add a significant contribution to the comprehension of infantile spasms (IS) and hypsarrhythmia. Functional MRI and magnetoencephalography (MEG) are two noninvasive tools that can be used in young children with IS. In the past two decades, interesting data about IS have emerged from functional MRI and MEG studies. Regarding their clinical utility, MEG has supported the concept that epileptic spasms can have a focal origin. Moreover, MEG might contribute to the localization of the epileptogenic zone in children with IS under investigation for epilepsy surgery. Functional MRI data have contributed to improve the knowledge about the physiopathology of IS and hypsarrhythmia. It has demonstrated abnormal brainstem involvement during the high-amplitude slow waves of hypsarrhythmia and cortical involvement during the epileptiform discharges. Since the feasibility of these techniques has been demonstrated in infants, it is possible that, in the future, larger functional MRI and MEG studies might contribute to the treatment and the definition of the long-term prognosis of children with IS.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2022), Vol. 39, No. 7 (35323155) (0 citations)

Endoscopic Total Corpus Callosotomy and Pan Commissurotomy for Lennox-Gastaut Syndrome (2022)

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BACKGROUND Corpus callosotomy (CC) is a major disconnection procedure that functionally isolates the cerebral hemispheres, thereby interrupting the spread of epileptic activity from one hemisphere to the other. It is extremely useful in children suffering from non-localized drug refractory epilepsy, especially drop attacks. The technique has evolved from microscopic to minimally invasive endoscopic surgery. The extent of callosotomy also varies based on the institutional practices ranging from anterior 1/3[rd] to total corpus callosotomies (TCC). The performance of TCC in conjunction with anterior, posterior, and hippocampal commissurotomies was described for the first time by the senior author from our institution.

OBJECTIVE To describe the technique of performing endoscopic total corpus callosotomy, and pan commissurotomy using the interhemispheric corridor.

METHODS A seven-year-old right-handed male child with seizure onset at the age of six months presented with three types of semiologies consisting of myoclonic jerks, frequent head drops and tonic posturing involving right upper and lower limbs with secondary generalization.

RESULTS Video electroencephalography (VEEG) revealed diffuse slowing of the background, and slow spike and wave pattern. Generalized paroxysmal fast activity (GPFA) was noted in the VEEG, suggestive of LGS. MRI brain revealed bilateral parieto-occipital gliosis and gross brain atrophy. Ictal SPECT localized to left temporo-occipital area, while magnetoencephalography revealed bilateral temporal localization. Patient

underwent TCC with pancommissurotomy. The patient was seizure-free (ILAE Class 3) at one-year follow up with no drop attacks, and significant reduction noted in other seizure types.

CONCLUSION Endoscopic corpus callosotomy and pan commissurotomy using the interhemispheric corridor is an elegant and minimally invasive technique best suited for appropriately selected children with refractory epilepsy.

Keywords: Anterior commissure, hippocampal commissure, interhemispheric approach, minimally invasive epilepsy surgery, posterior commissure

Neurology India (2022), Vol. 70, No. 1 (35263855) (1 citation)

Epidemic models characterize seizure propagation and the effects of epilepsy surgery in individualized brain networks based on MEG and invasive EEG recordings (2022)

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ABSTRACT Epilepsy surgery is the treatment of choice for drug-resistant epilepsy patients. However, seizure-freedom is currently achieved in only 2/3 of the patients after surgery. In this study we have developed an individualized computational model based on MEG brain networks to explore seizure propagation and the efficacy of different virtual resections. Eventually, the goal is to obtain individualized models to optimize resection strategy and outcome. We have modelled seizure propagation as an epidemic process using the susceptible-infected (SI) model on individual brain networks derived from presurgical MEG. We included 10 patients who had received epilepsy surgery and for whom the surgery outcome at least one year after surgery was known. The model parameters were tuned in in order to reproduce the patient-specific seizure propagation patterns as recorded with invasive EEG. We defined a personalized search algorithm that combined structural and dynamical information to find resections that maximally decreased seizure propagation for a given resection size. The optimal resection for each patient was defined as the smallest resection leading to at least a 90% reduction in seizure propagation. The individualized model reproduced the basic aspects of seizure propagation for 9 out of 10 patients when using the resection area as the origin of epidemic spreading, and for 10 out of 10 patients with an alternative definition of the seed region. We found that, for 7 patients, the optimal resection was smaller than the resection area, and for 4 patients we also found that a resection smaller than the resection area could lead to a 100% decrease in propagation. Moreover, for two cases these alternative resections included nodes outside the resection area. Epidemic spreading models fitted with patient specific data can capture the fundamental aspects of clinically observed seizure propagation, and can be used to test virtual resections in silico. Combined with optimization algorithms, smaller or alternative resection strategies, that are individually targeted for each patient, can be determined with the ultimate goal to improve surgery outcome. MEG-based networks can provide a good approximation of structural connectivity for computational models of seizure propagation, and facilitate their clinical use.

Scientific reports (2022), Vol. 12, No. 1 (35260657) (0 citations)

Interictal epileptiform discharges in focal epilepsy are preceded by increase in low-frequency oscillations (2022)

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OBJECTIVE Interictal epileptiform discharges (IEDs) constitute a diagnostic signature of epilepsy. These events reflect epileptogenic hypersynchronization. Previous studies indicated that IEDs arise from slow neuronal activation accompanied by metabolic and hemodynamic changes. These might induce cortical inhibition followed hypersynchronization at IED onset. As cortical inhibition is mediated by low-frequency oscillations, we aimed to analyze the role of low-frequency oscillations prior the IED using magnetencephalography (MEG).

METHODS Low-frequency (1-8 Hz) oscillations pre-IED ([-1000 milliseconds (ms), IED onset]) were analyzed using MEG in 14 focal epilepsy patients (median age = 23 years, range = 7-46 age). Occurrence of local pre-IED oscillations was analyzed using Beamformer Dynamical Imaging of Coherent Sources (DICS) and event-related desynchronization/synchronization (ERD-ERS) maps constructed using cluster-based permutation tests. The development of pre-IED oscillations was characterized using Hilbert transformation.

RESULTS All patients exhibited statistically significant increase in delta (1-4 Hz) and/or theta (4-8 Hz) oscillations pre-IED compared to baseline [-2000 ms, -1000 ms]. Furthermore, all patients exhibited low-frequency power increase up to IED onset.

CONCLUSIONS We demonstrated consistently occurring, low-frequency oscillations prior to IED onset.

SIGNIFICANCE As low-frequency activity mediates cortical inhibition, our study demonstrates that a focal inhibition precedes hypersynchronization at IED onset.

Keywords: Epilepsy, Interictal epileptiform discharges, Low-frequency oscillations, Magnetoencephalography, Synchronization

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2022), Vol. 136 (35217349) (2 citations)

Virtual intracranial EEG signals reconstructed from MEG with potential for epilepsy surgery (2022)

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ABSTRACT Modelling the interactions that arise from neural dynamics in seizure genesis is challenging but important in the effort to improve the success of epilepsy surgery. Dynamical network models developed from physiological evidence offer insights into rapidly evolving brain networks in the epileptic seizure. A limitation of previous studies in this field is the dependence on invasive cortical recordings with constrained spatial sampling of brain regions that might be involved in seizure dynamics. Here, we propose virtual intracranial electroencephalography (ViEEG), which combines non-invasive ictal magnetoencephalographic imaging (MEG), dynamical network models and a virtual resection technique. In this proof-of-concept study, we show that ViEEG signals reconstructed from MEG alone preserve critical temporospatial character-

istics for dynamical approaches to identify brain areas involved in seizure generation. We show the non-invasive ViEEG approach may have some advantage over intracranial electroencephalography (iEEG). Future work may be designed to test the potential of the virtual iEEG approach for use in surgical management of epilepsy.

Nature communications (2022), Vol. 13, No. 1 (35194035) (4 citations)

Focal Cortical Dysplasia and Generalized Epileptiform Discharges: Case Report and Literature Review (2021)

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BACKGROUND Focal epilepsy can have a varied etiology, including malformations of cortical development (MCD), that can often be detected by Magnetic Resonance Imaging (MRI).Here we show a distinct characteristic of two forms of MCDs on MRI, with two tight dipole clusters in her MEG magnetoencephalography study, in a patient with electroencephalography (EEG) features of generalized epilepsy.

CASE REPORT This is a case presentation of a 20 years old female with epilepsy, found to have upon EMU admission two pathologies (FCD, heterotropia) over the right side near the collateral sulcus, and two tight clusters of dipoles over the right parietal and left temporo-parietal region, with generalized inter ictal discharges in her EEG. FCD is a common etiology of medically intractable seizures and usually in EEG it will show either: pseudo-periodic spikes or rhythmic spikes, poly-spike or repetitive electrographic seizures or a brief discharge of fast rhythmic activity, atypical presentation with generalized epileptiform discharges were rarely reported.

CONCLUSION The presence of MCD does not preclude a patient from having other types of epilepsy. Generalized epilepsy and focal related epilepsy have a distinct pathophysiology.

Keywords: EEG, Epilepsy, MEG, MRI, focal cortical dysplasia

Medical archives (Sarajevo, Bosnia and Herzegovina) (2021), Vol. 75, No. 6 (35169375) (0 citations)

Assessment of Effective Network Connectivity among MEG None Contaminated Epileptic Transitory Events (2021)

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ABSTRACT Characterizing epileptogenic zones EZ (sources responsible of excessive discharges) would assist a neurologist during epilepsy diagnosis. Locating efficiently these abnormal sources among magnetoencephalography (MEG) biomarker is obtained by several inverse problem techniques. These techniques present different assumptions and particular epileptic network connectivity. Here, we proposed to evaluate performances of distributed inverse problem in defining EZ. First, we applied an advanced technique based on Singular Value Decomposition (SVD) to recover only pure transitory activities (interictal epileptiform discharges). We evaluated our technique's robustness in separation between transitory and ripples versus frequency range, transitory shapes, and signal to noise ratio on simulated data (depicting both epileptic biomarkers and respecting time series and spectral properties of realistic data). We validated our technique on MEG signal using detector precision on 5 patients. Then, we applied four methods of inverse problem to define cortical areas and neural generators of excessive discharges. We

computed network connectivity of each technique. Then, we confronted obtained noninvasive networks to intracerebral EEG transitory network connectivity using nodes in common, connection strength, distance metrics between concordant nodes of MEG and IEEG, and average propagation delay. Coherent Maximum Entropy on the Mean (cMEM) proved a high matching between MEG network connectivity and IEEG based on distance between active sources, followed by Exact low-resolution brain electromagnetic tomography (eLORETA), Dynamical Statistical Parametric Mapping (dSPM), and Minimum norm estimation (MNE). Clinical performance was interesting for entire methods providing in an average of 73.5% of active sources detected in depth and seen in MEG, and vice versa, about 77.15% of active sources were detected from MEG and seen in IEEG. Investigated problem techniques succeed at least in finding one part of seizure onset zone. dSPM and eLORETA depict the highest connection strength among all techniques. Propagation delay varies in this range [18, 25]ms, knowing that eLORETA ensures the lowest propagation delay (18 ms) and the closet one to IEEG propagation delay.

Computational and mathematical methods in medicine (2021), Vol. 2021 (34992674) (0 citations)

Mapping Functional Connectivity of Epileptogenic Networks through Virtual Implantation (2021)

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ABSTRACT Children with medically refractory epilepsy (MRE) require resective neurosurgery to achieve seizure freedom, whose success depends on accurate delineation of the epileptogenic zone (EZ). Functional connectivity (FC) can assess the extent of epileptic brain networks since intracranial EEG (icEEG) studies have shown its link to the EZ and predictive value for surgical outcome in these patients. Here, we propose a new noninvasive method based on magnetoencephalography (MEG) and high-density (HD-EEG) data that estimates FC metrics at the source level through an "implantation" of virtual sensors (VSs). We analyzed MEG, HD-EEG, and icEEG data from eight children with MRE who underwent surgery having good outcome and performed source localization (beamformer) on noninvasive data to build VSs at the icEEG electrode locations. We analyzed data with and without Interictal Epileptiform Discharges (IEDs) in different frequency bands, and computed the following FC matrices: Amplitude Envelope Correlation (AEC), Correlation (CORR), and Phase Locking Value (PLV). Each matrix was used to generate a graph using Minimum Spanning Tree (MST), and for each node (i.e., each sensor) we computed four centrality measures: betweenness, closeness, degree, and eigenvector. We tested the reliability of VSs measures with respect to icEEG (regarded as benchmark) via linear correlation, and compared FC values inside vs. outside resection. We observed higher FC inside than outside resection ($p<0.05$) for AEC [alpha (8-12 Hz), beta (12-30 Hz), and broadband (1-50 Hz)] on data with IEDs and AEC theta (4-8 Hz) on data without IEDs for icEEG, AEC broadband (1-50 Hz) on data without IEDs for MEG-VSs, as well as for all centrality measures of icEEG and MEG/HD-EEG-VSs. Additionally, icEEG and VSs metrics presented high correlation (0.6-0.9, $p<0.05$). Our data support the notion that the proposed method can potentially replicate the icEEG ability to map the epileptogenic network in children with MRE. Clinical Relevance - The estimation of FC with noninvasive techniques, such as MEG and HD-EEG, via VSs is a promising tool that would help the presurgical evaluation by delineating the EZ without waiting for a seizure to occur, and potentially improve the surgical outcome of patients with MRE undergoing surgery.

Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference (2021), Vol. 2021 (34891320) (0 citations)

Imaging the extent and location of spatiotemporally distributed epileptiform sources from MEG measurements (2022)

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ABSTRACT Non-invasive MEG/EEG source imaging provides valuable information about the epileptogenic brain areas which can be used to aid presurgical planning in focal epilepsy patients suffering from drug-resistant seizures. However, the source extent estimation for electrophysiological source imaging remains to be a challenge and is usually largely dependent on subjective choice. Our recently developed algorithm, fast spatiotemporal iteratively reweighted edge sparsity minimization (FAST-IRES) strategy, has been shown to objectively estimate extended sources from EEG recording, while it has not been applied to MEG recordings. In this work, through extensive numerical experiments and real data analysis in a group of focal drug-resistant epilepsy patients' interictal spikes, we demonstrated the ability of FAST-IRES algorithm to image the location and extent of underlying epilepsy sources from MEG measurements. Our results indicate the merits of FAST-IRES in imaging the location and extent of epilepsy sources for pre-surgical evaluation from MEG measurements.

Keywords: Electrophysiological source imaging (ESI), Epilepsy, Magnetoencephalography (MEG), Source extent imaging

NeuroImage. Clinical (2022), Vol. 33 (34864288) (1 citation)

Low density electrical source imaging of the ictal onset zone in the surgical evaluation of children with epilepsy (2021)

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PURPOSE To investigate the utility of Low Density (LD) Electrical Source Imaging (ESI) to model the ictal onset zone (IOZ) for the surgical work up of children with medically refractory epilepsy.

METHODS This was a retrospective review of 12 patients from a district and regional pediatric epilepsy center, who underwent focal resections between 2014 and 2019. ESI was generated using the Curry 8 software, incorporating T1 Magnetic Resonance Imaging (MRI) scans and scalp electroencephalogram (EEG) recordings. Concordance of the ictal LD-ESI localizations to the epileptogenic zone was assessed by comparing the location of the ictal LD-ESI to the focal resection margins on neuroimaging and noting the post-operative outcomes at one year. Localizations determined by ictal LD-ESI were also compared to interictal LD-ESI, positron emission tomography (FDG-PET) and interictal magnetoencephalography (MEG).

RESULTS Ictal ESI correctly localized the ictal onset zone in 4/6 patients, with all four being seizure free at one year. Similarly, interictal ESI localized the irritative zone in 7/9 patients with focal resections, with 6/7 being seizure free at one year. Additionally, we observed ictal ESI to be concordant to interictal ESI in 5/6 patients. Ictal ESI and interictal ESI were concordant to interictal MEG in 3/6 patients. Ictal ESI was concordant with FDG-PET in 6/7 cases.

CONCLUSION IOZ source localization through LD-ESI is a promising complementary method of assessing the epileptogenic focus in children. These findings may support the inclusion of ictal LD-ESI within the presurgical evaluation of children to supplement current diagnostic tools.

Keyword: Ictal Low Density Electrical Source Imaging

Epilepsy research (2021), Vol. 178 (34784573) (2 citations)

Underutilization of advanced presurgical studies and high rates of vagus nerve stimulation for drug-resistant epilepsy: a single-center experience and recommendations (2022)

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INTRODUCTION Epilepsy surgery continues to be profoundly underutilized despite its safety and effectiveness. We sought to investigate factors that may contribute to this phenomenon, with a particular focus on the antecedent underutilization of appropriate preoperative studies.

METHODS We reviewed patient data from a pediatric epilepsy clinic over an 18-month period. Patients with drug-resistant epilepsy (DRE) were categorized according to brain magnetic resonance imaging (MRI) findings (lesional, MRI-negative, or multifocal abnormalities) and type of epilepsy diagnosis based on semiology and electroencephalography (EEG) (focal or generalized). We then analyzed the rates of diagnostic test utilization, surgical referral, and subsequent epilepsy surgery as well as vagus nerve stimulation (VNS).

RESULTS Of the 249 patients with a diagnosis of epilepsy, 138 (55.4%) were found to have DRE. Excluding the 10 patients with DRE who did not undergo MRI, 76 patients (59.4%) were found to be MRI-negative (non-lesional epilepsy), 37 patients (28.9%) were found to have multifocal abnormalities, and 15 patients (11.7%) were found to have a single epileptogenic lesion on MRI (lesional epilepsy). Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) were each completed in nine patients (7.0%) and magnetoencephalography (MEG) in four patients (3.1%). Despite the low utilization rate of adjunctive studies, over half (56.3%) ultimately underwent VNS alone, and 8.6% ultimately underwent definitive intracranial resection or disconnection surgery.

CONCLUSIONS The underutilization of appropriate non-invasive, presurgical testing in patients with focal DRE may in part explain the continued underutilization of definitive, resective/disconnective surgery. For patients without access to a high-volume, multidisciplinary surgical epilepsy center, adjunctive presurgical studies [e.g., PET, SPECT, MEG, electrical source imaging (ESI), EEG-functional magnetic resonance imaging (fMRI)], even when available, are rarely ordered, and this may contribute to excessive rates of VNS in lieu of definitive intracranial surgery.

Keywords: DRE, MEG, PET, Preoperative studies, SPECT, Seizure surgery

Acta neurochirurgica (2022), Vol. 164, No. 2 (34773497) (1 citation)

Resting-State MEG Source Space Network Metrics Associated with the Duration of Temporal Lobe Epilepsy (2021)

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ABSTRACT To evaluate the relationship between the network metrics of 68 brain regions and duration of temporal lobe epilepsy (TLE). Magnetoencephalography (MEG) data from 53 patients with TLE (28 left TLE, 25 right TLE) were recorded between seizures at resting state and analyzed in six frequency bands: delta (0.1-4 Hz), theta (4-8 Hz), lower alpha (8-10 Hz), upper alpha (10-13 Hz), beta (13-30 Hz), and lower gamma (30-48 Hz). Three local network metrics, betweenness centrality, nodal degree, and nodal efficiency, were chosen to analyze the functional brain network. In Left, Right, and All (Left + Right) TLE groups, different metrics provide significant positive or negative correlations with the duration of TLE, in different frequency bands, and in different brain regions. In the Left TLE group, significant correlation between TLE duration and metric exists in the delta, beta, or lower gamma band, with network betweenness centrality, nodal degree, or nodal efficiency, in left caudal middle frontal, left middle temporal, or left supramarginal. In the Right TLE group, significant correlation exists in lower gamma or delta band, with nodal degree, or nodal efficiency, in left precuneus or right temporal pole. In the All TLE group, the significant correlation exists in delta, theta, beta, or lower gamma band, with nodal degree, or betweenness centrality, in either left or right hemisphere. Network metrics for some specific brain regions changed in patients with TLE as the duration of their TLE increased. Further researching these changes may be important for studying the pathogenesis, presurgical evaluation, and clinical treatment of long-term TLE.

Keywords: Brain network, Functional connectivity, Magnetoencephalography, Temporal lobe epilepsy

Brain topography (2021), Vol. 34, No. 6 (34652579) (0 citations)

[[18]F]FDG PET/MRI and magnetoencephalography may improve presurgical localization of temporal lobe epilepsy (2022)

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OBJECTIVES To evaluate the clinical value of the combination of [[18]F]FDG PET/MRI and magnetoencephalography (MEG) ([[18]F]FDG PET/MRI/MEG) in localizing the epileptogenic zone (EZ) in temporal lobe epilepsy (TLE) patients.

METHODS Seventy-three patients with localization-related TLE who underwent [[18]F]FDG PET/MRI and MEG were enrolled retrospectively. PET/MRI images were interpreted by two radiologists; the focal hypometabolism on PET was identified using statistical parametric mapping (SPM). MEG spike sources were co-registered onto T1-weighted sequence and analyzed by Neuromag software. The clinical value of [[18]F]FDG PET/MRI, MEG, and PET/MRI/MEG in locating the EZ was assessed using cortical resection and surgical outcomes as criteria. The correlations between surgical outcomes and modalities concordant or non-concordant with cortical resection were analyzed.

RESULTS For 46.6% (34/73) of patients, MRI showed definitely structural abnormality concordant with surgical resection. SPM results of [[18]F]FDG PET showed focal temporal lobe hypometabolism concordant with surgical resection in 67.1% (49/73) of patients, while the concordant cases increased to 82.2% (60/73) patients with simultaneous MRI co-registration. MEG was concordant with surgical resection in 71.2% (52/73) of patients. The lobar localization was defined in 94.5% (69/73) of patients by the [[18]F]FDG PET/MRI/MEG. The results of PET/MRI/MEG concordance with surgical resection were significantly higher than that of

PET/MRI or MEG ($\chi[2] = 13.948$, $p < 0.001$; $\chi[2] = 5.393$, $p = 0.020$). The results of PET/MRI/MEG cortical resection concordance with surgical outcome were shown to be better than PET/MRI or MEG ($\chi[2] = 6.695$, $p = 0.012$; $\chi[2] = 16.991$, $p < 0.0001$).

CONCLUSIONS Presurgical evaluation by [[18]F]FDG PET/MRI/MEG could improve the identification of the EZ in TLE and may further guide surgical decision-making.

KEY POINTS • Lobar localization was defined in 94.5% of patients by the [[18]F]FDG PET/MRI/MEG. • The results of PET/MRI/MEG concordance with surgical resection were significantly higher than that of PET/MRI or MEG alone. • The results of PET/MRI/MEG cortical resection concordance with surgical outcome were shown to be better than that of PET/MRI or MEG alone.

Keywords: Epilepsy, Magnetic resonance imaging, Magnetoencephalography, Positron emission tomography, Surgery

European radiology (2022), Vol. 32, No. 5 (34651211) (4 citations)

New interinstitutional, multimodal presurgical evaluation protocol associated with improved seizure freedom for poorly defined cases of focal epilepsy in children (2022)

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OBJECTIVE In an attempt to improve postsurgical seizure outcomes for poorly defined cases (PDCs) of pediatric focal epilepsy (i.e., those that are not visible or well defined on 3T MRI), the authors modified their presurgical evaluation strategy. Instead of relying on concordance between video-electroencephalography and 3T MRI and using functional imaging and intracranial recording in select cases, the authors systematically used a multimodal, 3-tiered investigation protocol that also involved new collaborations between their hospital, the Montreal Children's Hospital, and the Montreal Neurological Institute. In this study, the authors examined how their new strategy has impacted postsurgical outcomes. They hypothesized that it would improve postsurgical seizure outcomes, with the added benefit of identifying a subset of tests contributing the most.

METHODS Chart review was performed for children with PDCs who underwent resection following the new strategy (i.e., new protocol [NP]), and for the same number who underwent treatment previously (i.e., preprotocol [PP]); ≥ 1-year follow-up was required for inclusion. Well-defined, multifocal, and diffuse hemispheric cases were excluded. Preoperative demographics and clinical characteristics, resection volumes, and pathology, as well as seizure outcomes (Engel class Ia vs > Ia) at 1 year postsurgery and last follow-up were reviewed.

RESULTS Twenty-two consecutive NP patients were compared with 22 PP patients. There was no difference between the two groups for resection volumes, pathology, or preoperative characteristics, except that the NP group underwent more presurgical evaluation tests ($p < 0.001$). At 1 year postsurgery, 20 of 22 NP patients and 10 of 22 PP patients were seizure free (OR 11.81, 95% CI 2.00-69.68; $p = 0.006$). Magnetoencephalography and PET/MRI were associated with improved postsurgical

seizure outcomes, but both were highly correlated with the protocol group (i.e., independent test effects could not be demonstrated).

CONCLUSIONS A new presurgical evaluation strategy for children with PDCs of focal epilepsy led to improved postsurgical seizure freedom. No individual presurgical evaluation test was independently associated with improved outcome, suggesting that it may be the combined systematic protocol and new interinstitutional collaborations that makes the difference rather than any individual test.

Keywords: children, focal epilepsy, neuroimaging, outcomes, presurgical evaluation, protocol

Journal of neurosurgery. Pediatrics (2022), Vol. 29, No. 1 (34624842) (1 citation)

Localizing the Epileptogenic Zone with Novel Biomarkers (2021)

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ABSTRACT Several noninvasive methods, such as high-density EEG or magnetoencephalography, are currently used to delineate the epileptogenic zone (EZ) during the presurgical evaluation of patients with drug resistant epilepsy (DRE). Yet, none of these methods can reliably identify the EZ by their own. In most cases a multimodal approach is needed. Challenging cases often require the implantation of intracranial electrodes, either through stereo-taxic EEG or electrocorticography. Recently, a growing body of literature introduces novel biomarkers of epilepsy that can be used for analyzing both invasive as well as noninvasive electrophysiological data. Some of these biomarkers are able to delineate the EZ with high precision, augment the presurgical evaluation, and predict the surgical outcome of patients with DRE undergoing surgery. However, the use of these epilepsy biomarkers in clinical practice is limited. Here, we summarize and discuss the latest technological advances in the presurgical neurophysiological evaluation of children with DRE with emphasis on electric and magnetic source imaging, high frequency oscillations, and functional connectivity.

Seminars in pediatric neurology (2021), Vol. 39 (34620466) (3 citations)

Presurgical Evaluation Strategies for Intractable Epilepsy of Childhood (2021)

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ABSTRACT For children who continue to experience seizures despite treatment with antiseizure medications, epilepsy surgery can be considered. The goals of the presurgical evaluation are to determine the best surgical approach to render a good outcome. In patients with drug resistant focal epilepsy, the epileptogenic zone defines the minimal brain volume which must be resected for surgical success and to delineate the relationship of this region with functional cortex. A number of noninvasive tools for these tasks have emerged over the past decade, and existing technologies have been revised and improved. In this review, we examine the recent published evidence for these techniques, specifically as applied to the pediatric population. Discussed herein are the diagnostic value of methods such as video electroencephalography, magnetic resonance imaging, and supportive neuroimaging techniques including single photon emis-

sion tomography, photon emission tomography, and magnetoencephalography. Functional testing including functional magnetic resonance imaging, electrical stimulation mapping, and transcranial magnetic stimulation are considered in the context of pediatric epilepsy. The application of emerging techniques to preoperative testing such as source localization, image post-processing, and artificial intelligence is covered. We summarize the relative value of presurgical testing based on patient characteristics, including lesional or nonlesional MRI, temporal or extratemporal epilepsy, and other factors relevant in pediatric epilepsy such as pathological substrate and age.

Seminars in pediatric neurology (2021), Vol. 39 (34620457) (2 citations)

Cellular Substrates of Functional Network Integration and Memory in Temporal Lobe Epilepsy (2022)

Douw, Linda; Nissen, Ida A; Fitzsimmons, Sophie M D D; Santos, Fernando A N; Hillebrand, Arjan; van Straaten, Elisabeth C W; Stam, Cornelis J; De Witt Hamer, Philip C; Baayen, Johannes C; Klein, Martin; Reijneveld, Jaap C; Heyer, Djai B; Verhoog, Matthijs B; Wilbers, René; Hunt, Sarah; Mansvelder, Huibert D; Geurts, Jeroen J G; de Kock, Christiaan P J; Goriounova, Natalia A

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ABSTRACT Temporal lobe epilepsy (TLE) patients are at risk of memory deficits, which have been linked to functional network disturbances, particularly of integration of the default mode network (DMN). However, the cellular substrates of functional network integration are unknown. We leverage a unique cross-scale dataset of drug-resistant TLE patients (n = 31), who underwent pseudo resting-state functional magnetic resonance imaging (fMRI), resting-state magnetoencephalography (MEG) and/or neuropsychological testing before neurosurgery. fMRI and MEG underwent atlas-based connectivity analyses. Functional network centrality of the lateral middle temporal gyrus, part of the DMN, was used as a measure of local network integration. Subsequently, non-pathological cortical tissue from this region was used for single cell morphological and electrophysiological patch-clamp analysis, assessing integration in terms of total dendritic length and action potential rise speed. As could be hypothesized, greater network centrality related to better memory performance. Moreover, greater network centrality correlated with more integrative properties at the cellular level across patients. We conclude that individual differences in cognitively relevant functional network integration of a DMN region are mirrored by differences in cellular integrative properties of this region in TLE patients. These findings connect previously separate scales of investigation, increasing translational insight into focal pathology and large-scale network disturbances in TLE.

Keywords: action potential kinetics, cellular morphology, connectome, graph theory, resting-state fMRI

Cerebral cortex (New York, N.Y.: 1991) (2022), Vol. 32, No. 11 (34564728) (0 citations)

Cross-Frequency Coupling in Childhood Absence Epilepsy (2022)

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ABSTRACT Objective: Absence seizures are the prototypic primarily generalized seizures, but there is incomplete understanding regarding their generation and maintenance. A core network for absence seizures has been defined, including focal cortical and thalamic regions that have frequency-dependent interactions. The purpose of this study was to investigate within-frequency coupling and cross-frequency coupling (CFC) during human absence seizures, to identify key regions (hubs) within the absence network that contribute to propagation and maintenance. Methods: Thirteen children with new-onset and untreated childhood absence epilepsy had over 60 typical absence seizures during both electroencephalography-functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) recordings. The spatial map of the ictal network was defined using fMRI and used as prior information for MEG connectivity. A multilayer network approach was used to investigate within-frequency coupling and CFC for canonical frequency bands. A rigorous null-modeling approach was used to determine connections outside the noise floor. Results: Strong coupling between beta and gamma frequencies, within the left frontal cortex, and between the left frontal and right parietal regions was observed. There was also strong connectivity between left frontal and right parietal nodes within the gamma band. Multilayer versatility analysis identified a cluster of network hubs in the left frontal region. Interpretation: Cortical regions commonly identified as being critical for absence seizure generation (frontal cortex, precuneus) have strong CFC and within-frequency coupling between beta and gamma bands. As nonpharmacologic treatments, such as neuromodulation, become available for generalized epilepsies, detailed mechanistic understanding of how "diffuse" seizures are generated and maintained will be necessary to provide optimal outcomes.

Keywords: absence epilepsy, connectivity, cross-frequency coupling, magnetoencephalography

Brain connectivity (2022), Vol. 12, No. 5 (34405685) (4 citations)

MEG detection of high frequency oscillations and intracranial-EEG validation in pediatric epilepsy surgery (2021)

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OBJECTIVE To assess the feasibility of automatically detecting high frequency oscillations (HFOs) in magnetoencephalography (MEG) recordings in a group of ten paediatric epilepsy surgery patients who had undergone intracranial electroencephalography (iEEG).

METHODS A beamforming source-analysis method was used to construct virtual sensors and an automatic algorithm was applied to detect HFOs (80-250 Hz). We evaluated the concordance of MEG findings with the sources of iEEG HFOs, the clinically defined seizure onset zone (SOZ), the location of resected brain structures, and with post-operative outcome.

RESULTS In 8/9 patients there was good concordance between the sources of MEG HFOs and iEEG HFOs and

the SOZ. Significantly more HFOs were detected in iEEG relative to MEG $t(71) = 2.85$, $p < .05$. There was good concordance between sources of MEG HFOs and the resected area in patients with good and poor outcome, however HFOs were also detected outside of the resected area in patients with poor outcome.

CONCLUSION Our findings demonstrate the feasibility of automatically detecting HFOs non-invasively in MEG recordings in paediatric patients, and confirm compatibility of results with invasive recordings.

SIGNIFICANCE This approach provides support for the non-invasive detection of HFOs to aid surgical planning and potentially reduce the need for invasive monitoring, which is pertinent to paediatric patients.

Keywords: Automatic detection, Beamforming, Epilepsy, HFOs, Kurtosis, MEG, Paediatric age, iEEG

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2021), Vol. 132, No. 9 (34284249) (1 citation)

Functional reorganization of brain regions into a network in childhood absence epilepsy: A magnetoencephalography study (2021)

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OBJECTIVE Epilepsy is considered as a network disorder. However, it is unknown how normal brain activity develops into the highly synchronized discharging activity seen in disordered networks. This study aimed to explore the epilepsy brain network and the significant re-combined brain areas in childhood absence epilepsy (CAE).

METHODS Twenty-two children with CAE were recruited to study the neural source activity during ictal-onset and interictal periods at frequency bands of 1-30 Hz and 30-80 Hz with magnetoencephalography (MEG) scanning. Accumulated source imaging (ASI) was used to analyze the locations of neural source activity and peak source strength.

RESULTS Most of the participants had more active source activity locations in the ictal-onset period rather than in the interictal period, both at 1-30 Hz and 30-80 Hz. The frontal lobe (FL), the temporo-parietal junction (T-P), and the parietal lobe (PL) became the main active areas of source activity during the ictal period, while the precuneus (PC), cuneus, and thalamus were relatively inactive.

CONCLUSIONS Some brain areas become more excited and have increased source activity during seizures. These significant brain regions might be re-combined to form an epilepsy network that regulates the process of absence seizures.

SIGNIFICANCE The study confirmed that important brain regions are reorganized in an epilepsy network, which provides a basis for exploring the network mechanism of CAE development. Imaging findings may provide a reference for clinical characteristics.

Keywords: Childhood absence epilepsy, Default mode network, Epilepsy network, Functional reorganization, Magnetoencephalography, Multi-focal source activity

Epilepsy & behavior: E&B (2021), Vol. 122 (34246893) (2 citations)

Magnetoencephalography Imaging Reveals Abnormal Information Flow in Temporal Lobe Epilepsy (2022)

Kudo, Kiwamu; Morise, Hirofumi; Ranasinghe, Kamalini G; Mizuiri, Danielle; Bhutada, Abhishek S; Chen, Jessie; Findlay, Anne; Kirsch, Heidi E; Nagarajan, Srikantan S

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ABSTRACT Background/Introduction: Widespread network disruption has been hypothesized to be an important predictor of outcomes in patients with refractory temporal lobe epilepsy (TLE). Most studies examining functional network disruption in epilepsy have largely focused on the symmetric bidirectional metrics of the strength of network connections. However, a more complete description of network dysfunction impacts in epilepsy requires an investigation of the potentially more sensitive directional metrics of information flow. Methods: This study describes a whole-brain magnetoencephalography-imaging approach to examine resting-state directional information flow networks, quantified by phase-transfer entropy (PTE), in patients with TLE compared with healthy controls (HCs). Associations between PTE and clinical characteristics of epilepsy syndrome are also investigated. Results: Deficits of information flow were specific to alpha-band frequencies. In alpha band, while HCs exhibit a clear posterior-to-anterior directionality of information flow, in patients with TLE, this pattern of regional information outflow and inflow was significantly altered in the frontal and occipital regions. The changes in information flow within the alpha band in selected brain regions were correlated with interictal spike frequency and duration of epilepsy. Conclusions: Impaired information flow is an important dimension of network dysfunction associated with the pathophysiological mechanisms of TLE.

Keywords: atlas-based connectivity, epilepsy, magnetoencephalography, phase-transfer entropy

Brain connectivity (2022), Vol. 12, No. 4 (34210170) (2 citations)

Evaluation of Brain Network Properties in Patients with MRI-Negative Temporal Lobe Epilepsy: An MEG Study (2021)

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ABSTRACT Abnormal functional brain networks of temporal lobe epilepsy (TLE) patients with structural abnormalities may partially reflect structural lesions rather than either TLE per se or functional compensatory processes. In this study, we sought to investigate the brain-network properties of intractable TLE patients apart from the effects of structural abnormalities. The brain network properties of 20 left and 23 right MRI-negative TLE patients and 22 healthy controls were evaluated using magnetoencephalographic recordings in six main frequency bands. A slowing of oscillatory brain activity was observed for the left or right TLE group vs. healthy controls. The TLE groups presented significantly increased functional connectivity in the delta, theta, lower alpha and beta bands, and significantly greater values in the normalized clustering coefficient and path length, and significantly smaller values in the weighted small-world measure in the theta band when compared to healthy controls. Alterations in global and regional band powers can be attributed to spectral slowing in TLE patients. The brain

networks of TLE patients displayed abnormally high synchronization in multi-frequency bands and shifted toward a more regular architecture with worse network efficiency in the theta band. Without the contamination of structural lesions, these significant findings can be helpful for better understanding of the pathophysiological mechanism of TLE. The theta band can be considered as a preferred frequency band for investigating the brain-network dysfunction of MRI-negative intractable TLE patients.

Keywords: Brain network, Functional connectivity, Graph theory, MRI-negative, Magnetoencephalography, Temporal lobe epilepsy

Brain topography (2021), Vol. 34, No. 5 (34173926) (3 citations)

Magnetoencephalography to confirm epileptiform discharges mimicking small sharp spikes in temporal lobe epilepsy (2021)

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OBJECTIVE To determine whether magnetoencephalography (MEG) can identify epileptiform discharges mimicking small sharp spikes (SSSs) on scalp electroencephalography (EEG) in patients with temporal lobe epilepsy (TLE).

METHODS We retrospectively reviewed simultaneous scalp EEG and MEG recordings of 83 consecutive patients with TLE and 49 with extra-TLE (ETLE).

RESULTS SSSs in scalp EEG were detected in 15 (18.1%) of 83 TLE patients compared to only two (4.1%) of 49 ETLE patients (p = 0.029). Five of the 15 TLE patients had MEG spikes with concurrent SSSs in EEG, but neither of the 2 ETLE patients. Three of these 5 TLE patients had additional interictal epileptiform discharges (IEDs) in EEG and MEG. Equivalent current dipoles (ECDs) of MEG spikes with concurrent SSSs and IEDs showed no difference in temporal lobe localization and horizontal orientation, whereas ECD moments were smaller in MEG spikes with concurrent SSSs than those with IEDs.

CONCLUSIONS SSSs were more common in TLE than in ETLE. At least some morphologically diagnosed SSSs are true but low-amplitude epileptiform discharges in TLE which can be identified with simultaneous MEG.

SIGNIFICANCE Simultaneous MEG is useful to identify epileptiform discharges mimicking SSSs in patients with TLE.

Keywords: Benign epileptiform transients of sleep, Magnetoencephalography, Small sharp spikes, Temporal lobe epilepsy

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2021), Vol. 132, No. 8 (34130246) (0 citations)

Diagnostic added value of interictal magnetic source imaging in presurgical evaluation of persons with epilepsy: A prospective blinded study (2021)

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BACKGROUND AND PURPOSE In presurgical evaluation for epilepsy surgery, information is sourced from various imaging modalities to accurately localize the epileptogenic zone. Magnetoencephalography (MEG) is a newer noninvasive technique for localization. However, there is limited literature to evaluate if MEG provides additional advantage over the conventional imaging modalities in clinical decision making. The objective of this study was to assess the diagnostic added value of MEG in decision making before epilepsy surgery.

METHOD This was a prospective observational study. Patients underwent 3 h of recording in a MEG scanner, and the resulting localizations were compared with other complimentary investigations. Added value of MEG (considered separately from high-density electroencephalography) was defined as the frequency of cases in which (i) the information provided by magnetic source imaging (MSI) avoided implantation of intracranial electrodes and the patient was directly cleared for surgery, and (ii) MSI indicated additional substrates for implantation of intracranial electrodes. Postoperative seizure freedom was used as the diagnostic reference by which to measure the localizing accuracy of MSI.

RESULTS A total of 102 patients underwent epilepsy surgery. MEG provided nonredundant information, which contributed to deciding the course of surgery in 33% of the patients, and prevented intracranial recordings in 19%. A total of 76% of the patients underwent surgical resection in sublobes concordant with MSI localization, and the diagnostic odds ratio for good (Engel I) outcome in these patients was 2.3 (95% confidence interval 0.68, 7.86; p = 0.183) after long-term follow-up of 36 months.

CONCLUSION Magnetic source imaging yields additional useful information which can significantly alter as well as improve the surgical strategy for persons with epilepsy.

Keywords: diagnostic added value, drug-resistant epilepsy, electroencephalography, epilepsy, magnetoencephalography

European journal of neurology (2021), Vol. 28, No. 9 (34124810) (1 citation)

Magnetic source imaging in presurgical evaluation of paediatric focal drug-resistant epilepsy and its predictive value of surgical outcome in lesional cases: A single-centre experience from South India (2021)

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OBJECTIVE This study aims to evaluate the utility of magnetoencephalography in presurgical planning and in predicting post-surgical seizure outcome.

METHODS This study included a cohort of 231 children (1-18 years) with focal drug-resistant epilepsy who

underwent MEG as a part of their presurgical workup. Characteristics of MEG observations were described in all children. The concordance and agreement of Magnetic Source Imaging (MSI) of interictal discharges (IED) was estimated with either of the 3 subgroups - MRI lesion; presumed epileptogenic zone (EZ); or resection cavity. In operated children group, MEG dipole characteristics between good and poor outcome groups were assessed.

RESULTS A total of 153 cases (66.2%) showed frequent IEDs (60 spikes/60 min). Of the 173 cases where MSI showed clusters (74.9%), 151 had lesions and 22 were non-lesional. amongst patients with lesional epilepsy and MEG clusters, class I concordance (MEG localization either completely included or overlapped at least 60% with the MRI lesion) was seen in 60.92% with a Cohen's kappa of 0.608. In non-lesional epilepsy, class I concordance of MEG with presumed EZ was found in (81.81%) with an agreement of 0.317. Fifty-three children underwent surgery of whom 39 (73.58%) showed a good outcome (Engel I). In operated children, concordance between MEG focus and resection cavity was observed in 23 (58.97%) with good outcome and in 12 (86.72%) with poor outcome with no significant difference (p>0.05). However, MEG cluster regular organization and clusterectomy are associated with good seizure outcome postoperatively (p< 0.05). Presence of scatters were associated with poor outcome (p<0.05) in children with focal cortical dysplasia.

CONCLUSIONS MEG provides useful information that can serve as a biomarker for prognosticating the surgical outcome in paediatric epilepsy. Cluster removal and regular cluster organization shows predictive power in post-surgical prognostication in children and the presence of scatters predicts poor outcome in children with focal cortical dysplasia.

Keywords: Drug resistant epilepsy, Magnetoencephalography (MEG), Paediatric epilepsy surgery

Seizure (2021), Vol. 91 (34058605) (0 citations)

Heritability of Magnetoencephalography Phenotypes Among Patients With Genetic Generalized Epilepsy and Their Siblings (2021)

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OBJECTIVE To assess whether neuronal signals in patients with genetic generalized epilepsy (GGE) are heritable, we examined magnetoencephalography resting-state recordings in patients and their healthy siblings.

METHODS In a prospective, cross-sectional design, we investigated source-reconstructed power and functional connectivity in patients, siblings, and controls. We analyzed 5 minutes of cleaned and awake data without epileptiform discharges in 6 frequency bands (1-40 Hz). We further calculated intraclass correlations to estimate heritability for the imaging patterns within families.

RESULTS Compared with controls (n = 45), patients with GGE (n = 25) showed widespread increased functional connectivity (θ to γ frequency bands) and power (δ to γ frequency bands) across the spectrum. Siblings (n = 18) fell between the levels of patients and controls. Heritability of the imaging metrics was observed in

regions where patients strongly differed from controls, mainly in β frequencies, but also for δ and θ power. Network connectivity in GGE was heritable in frontal, central, and inferior parietal brain areas and power in central, temporo-parietal, and subcortical structures. Presence of generalized spike-wave activity during recordings and medication were associated with the network patterns, whereas other clinical factors such as age at onset, disease duration, or seizure control were not.

CONCLUSION Metrics of brain oscillations are well suited to characterize GGE and likely relate to genetic factors rather than the active disease or treatment. High power and connectivity levels co-segregated in patients with GGE and healthy siblings, predominantly in the β band, representing an endophenotype of GGE.

Neurology (2021), Vol. 97, No. 2 (34045271) (5 citations)

Detrended fluctuation analysis in the presurgical evaluation of parietal lobe epilepsy patients (2021)

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OBJECTIVE To examine the usability of long-range temporal correlations (LRTCs) in non-invasive localization of the epileptogenic zone (EZ) in refractory parietal lobe epilepsy (RPLE) patients.

METHODS We analyzed 10 RPLE patients who had presurgical MEG and underwent epilepsy surgery. We quantified LRTCs with detrended fluctuation analysis (DFA) at four frequency bands for 200 cortical regions estimated using individual source models. We correlated individually the DFA maps to the distance from the resection area and from cortical locations of interictal epileptiform discharges (IEDs). Additionally, three clinical experts inspected the DFA maps to visually assess the most likely EZ locations.

RESULTS The DFA maps correlated with the distance to resection area in patients with type II focal cortical dysplasia (FCD) ($p<0.05$), but not in other etiologies. Similarly, the DFA maps correlated with the IED locations only in the FCD II patients. Visual analysis of the DFA maps showed high interobserver agreement and accuracy in FCD patients in assigning the affected hemisphere and lobe.

CONCLUSIONS Aberrant LRTCs correlate with the resection areas and IED locations.

SIGNIFICANCE This methodological pilot study demonstrates the feasibility of approximating cortical LRTCs from MEG that may aid in the EZ localization and provide new non-invasive insight into the presurgical evaluation of epilepsy.

Keywords: Detrended fluctuation analysis, Epilepsy surgery, Long-range temporal correlation, MEG

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2021), Vol. 132, No. 7 (34030053) (1 citation)

How cerebral cortex protects itself from interictal spikes: The alpha/beta inhibition mechanism (2021)

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ABSTRACT Interactions between interictal epileptiform discharges (IEDs) and distant cortical regions subserve potential effects on cognition of patients with focal epilepsy. We hypothesize that "healthy" brain areas at a distance from the epileptic focus may respond to the interference of IEDs by generating inhibitory alpha and beta oscillations. We predict that more prominent alpha-beta oscillations can be found in patients with less impaired neurocognitive profile. We performed a source imaging magnetoencephalography study, including 41 focal epilepsy patients: 21 with frontal lobe epilepsy (FLE) and 20 with mesial temporal lobe epilepsy. We investigated the effect of anterior (i.e., frontal and temporal) IEDs on the oscillatory pattern over posterior head regions. We compared cortical oscillations (5-80 Hz) temporally linked to 3,749 IEDs (1,945 frontal and 1,803 temporal) versus an equal number of IED-free segments. We correlated results from IED triggered oscillations to global neurocognitive performance. Only frontal IEDs triggered alpha-beta oscillations over posterior head regions. IEDs with higher amplitude triggered alpha-beta oscillations of higher magnitude. The intensity of posterior head region alpha-beta oscillations significantly correlated with a better neuropsychological profile. Our study demonstrated that cerebral cortex protects itself from IEDs with generation of inhibitory alpha-beta oscillations at distant cortical regions. The association of more prominent oscillations with a better cognitive status suggests that this mechanism might play a role in determining the cognitive resilience in patients with FLE.

Keywords: alpha, beta, epilepsy, inhibition, interictal epileptiform discharges, magnetoencephalography, oscillations

Human brain mapping (2021), Vol. 42, No. 11 (34002916) (6 citations)

Neuromagnetic high frequency spikes are a new and noninvasive biomarker for localization of epileptogenic zones (2021)

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OBJECTIVE One barrier hindering high frequency brain signals (HFBS, >80 Hz) from wide clinical applications is that the brain generates both pathological and physiological HFBS. This study was to find specific biomarkers for localizing epileptogenic zones (EZs).

METHODS Twenty three children with drug-resistant epilepsy and age/sex matched healthy controls were studied with magnetoencephalography (MEG). High frequency oscillations (HFOs, > 4 oscillatory waveforms) and high frequency spikes (HFSs, > 1 spiky or sharp waveforms) in 80-250 Hz and 250-600 Hz bands were blindly detected with an artificial intelligence method and validated with visual inspection. The magnitude of HFOs and HFSs were quantified with spectral analyses. Sources of HFSs and HFOs were localized and compared with clinical EZs determined by invasive recordings and surgical outcomes.

RESULTS HFOs in 80-250 Hz and 250-600 Hz were identified in both epilepsy patients (18/23, 12/23, respec-

tively) and healthy controls (6/23, 4/23, respectively). HFSs in 80-250 Hz and 250-600 Hz were detected in patients (16/23, 11/23, respectively) but not in healthy controls. A combination of HFOs and HFSs localized EZs for 22 (22/23, 96%) patients.

CONCLUSIONS The results indicate, for the first time, that HFSs are a newer and more specific biomarker than HFOs for localizing EZs because HFOs appeared in both epilepsy patients and healthy controls while HFSs appeared only in epilepsy patients.

Keywords: Epilepsy, High frequency activity, High frequency spike, High-frequency oscillation, Magnetic Source Imaging, Magnetoencephalography

Seizure (2021), Vol. 89 (33975080) (0 citations)

Magnetoencephalography for epileptic focus localization based on Tucker decomposition with ripple window (2021)

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AIMS To improve the Magnetoencephalography (MEG) spatial localization precision of focal epileptic.

METHODS 306-channel simulated or real clinical MEG is estimated as a lower-dimensional tensor by Tucker decomposition based on Higher-order orthogonal iteration (HOOI) before the inverse problem using linearly constraint minimum variance (LCMV). For simulated MEG data, the proposed method is compared with dynamic imaging of coherent sources (DICS), multiple signal classification (MUSIC), and LCMV. For clinical real MEG of 31 epileptic patients, the ripples (80-250 Hz) were detected to compare the source location precision with spikes using the proposed method or the dipole-fitting method.

RESULTS The experimental results showed that the positional accuracy of the proposed method was higher than that of LCMV, DICS, and MUSIC for simulation data. For clinical real MEG data, the positional accuracy of the proposed method was higher than that of dipole-fitting regardless of whether the time window was ripple window or spike window. Also, the positional accuracy of the ripple window was higher than that of the spike window regardless of whether the source location method was the proposed method or the dipole-fitting method. For both shallow and deep sources, the proposed method provided effective performance.

CONCLUSION Tucker estimation of MEG for source imaging by ripple window is a promising approach toward the presurgical evaluation of epileptics.

Keywords: MEG, focal epileptic, higher-order orthogonal iteration, ripple, source imaging, tucker decomposition

CNS neuroscience & therapeutics (2021), Vol. 27, No. 7 (33942534) (0 citations)

Recent Advances in Neuroimaging of Epilepsy (2021)

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ABSTRACT Human neuroimaging has had a major impact on the biological understanding of epilepsy and the relationship between pathophysiology, seizure management, and outcomes. This review highlights notable recent advancements in hardware, sequences, methods, analyses, and applications of human neuroimaging techniques utilized to assess epilepsy. These structural, functional, and metabolic assessments include magnetic resonance imaging (MRI), positron emission tomography (PET), and magnetoencephalog-

raphy (MEG). Advancements that highlight non-invasive neuroimaging techniques used to study the whole brain are emphasized due to the advantages these provide in clinical and research applications. Thus, topics range across presurgical evaluations, understanding of epilepsy as a network disorder, and the interactions between epilepsy and comorbidities. New techniques and approaches are discussed which are expected to emerge into the mainstream within the next decade and impact our understanding of epilepsies. Further, an increasing breadth of investigations includes the interplay between epilepsy, mental health comorbidities, and aberrant brain networks. In the final section of this review, we focus on neuroimaging studies that assess bidirectional relationships between mental health comorbidities and epilepsy as a model for better understanding of the commonalities between both conditions.

Keywords: Epilepsy, Mental health, Network disorder, Neuroimaging, Neurosurgery

Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics (2021), Vol. 18, No. 2 (33942270) (9 citations)

Presurgical accuracy of dipole clustering in MRI-negative pediatric patients with epilepsy: Validation against intracranial EEG and resection (2022)

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OBJECTIVE To assess the utility of interictal magnetic and electric source imaging (MSI and ESI) using dipole clustering in magnetic resonance imaging (MRI)-negative patients with drug resistant epilepsy (DRE).

METHODS We localized spikes in low-density (LD-EEG) and high-density (HD-EEG) electroencephalography as well as magnetoencephalography (MEG) recordings using dipoles from 11 pediatric patients. We computed each dipole's level of clustering and used it to discriminate between clustered and scattered dipoles. For each dipole, we computed the distance from seizure onset zone (SOZ) and irritative zone (IZ) defined by intracranial EEG. Finally, we assessed whether dipoles proximity to resection was predictive of outcome.

RESULTS LD-EEG had lower clusterness compared to HD-EEG and MEG ($p < 0.05$). For all modalities, clustered dipoles showed higher proximity to SOZ and IZ than scattered ($p < 0.001$). Resection percentage was higher

in optimal vs. suboptimal outcome patients ($p < 0.001$); their proximity to resection was correlated to outcome ($p < 0.001$). No difference in resection percentage was seen for scattered dipoles between groups.

CONCLUSION MSI and ESI dipole clustering helps to localize the SOZ and IZ and facilitate the prognostic assessment of MRI-negative patients with DRE.

SIGNIFICANCE Assessing the MSI and ESI clustering allows recognizing epileptogenic areas whose removal is associated with optimal outcome.

Keywords: Dipole clusterness, Electric source imaging, Epilepsy surgery, Localization, Magnetic source imaging, Negative MRI

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2022), Vol. 141 (33875376) (9 citations)

A review of magnetoencephalography use in pediatric epilepsy: an update on best practice (2021)

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ABSTRACT Introduction: Magnetoencephalography (MEG) is a noninvasive technique that is used for presurgical evaluation of children with drug-resistant epilepsy (DRE).Areas covered: The contributions of MEG for localizing the epileptogenic zone are discussed, in particular in extra-temporal lobe epilepsy and focal cortical dysplasia, which are common in children, as well as in difficult to localize epilepsy such as operculo-insular epilepsy. Further, the authors review current evidence on MEG for mapping eloquent cortex, its performance, application in clinical practice, and potential challenges.Expert opinion: MEG could change the clinical management of children with DRE by directing placement of intracranial electrodes thereby enhancing their yield. With improved identification of a circumscribed epileptogenic zone, MEG could render more patients as suitable candidates for epilepsy surgery and increase utilization of surgery.

Keywords: Drug-resistant epilepsy, eloquent cortex mapping, epilepsy surgery evaluation, epileptogenic zone, magnetoencephalography

Expert review of neurotherapeutics (2021), Vol. 21, No. 11 (33780318) (1 citation)

Pediatric Epilepsy Surgery: Indications and Evaluation (2021)

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ABSTRACT Epilepsy is a common neurological condition in children. It is usually amenable to drug therapy. However, nearly one-third of patients may be refractory to antiseizure drugs. Poor compliance and nonepileptic events should be ruled out as possible causes of drug-resistant epilepsy (DRE). After failing adequate trials of two appropriate antiseizure drugs, patients with focal DRE or poorly classifiable epilepsy or epileptic encephalopathy with focal electro-clinical features should be worked up for surgical candidacy. A randomized controlled trial provided a class I evidence for epilepsy surgery in pediatric DRE. Pre-surgical screening workup typically includes a high-resolution epilepsy protocol brain magnetic resonance imaging (MRI) and a high-quality in-patient video electroencepha-

lography evaluation. Advanced investigations such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetoencephalography (MEG) may be required in selected cases especially when brain MRI is normal, and further evidence for anatomo-electro-clinical concordance is necessary to refine candidacy for surgery and surgical strategy. Some children may also need functional MRI to map eloquent regions of interest such as motor, sensory, and language functions to avoid unacceptable neurological deficits after surgery. Selected children may need invasive long-term electroencephalographic monitoring using stereotactically implanted intracranial depth electrodes or subdural grids. Surgical options include resective surgeries (lesionectomy, lobectomy, multilobar resections) and disconnective surgeries (corpus callosotomy, etc.) with the potential to obtain seizure freedom. Other surgical procedures, typically considered to be palliative are neuromodulation [deep brain stimulation (DBS), vagal nerve stimulation (VNS), and responsive neural stimulation (RNS)]. DBS and RNS are currently not approved in children. Pediatric DRE should be evaluated early considering the risk of epileptic encephalopathy and negative impact on cognition.

Keywords: Children, Drug-resistant epilepsy, Epilepsy surgery, Pre-surgical workup

Indian journal of pediatrics (2021), Vol. 88, No. 10 (33740232) (7 citations)

Comprehensive genetic, clinical and electrophysiological studies of familial cortical myoclonic tremor with epilepsy 1 highlight the role of gene configurations (2021)

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OBJECTIVES Two configurations of TTTTA/TTTCA expansion in SAMD12 have been identified in familial cortical myoclonic tremor with epilepsy type 1 (FCMTE1). This study investigated the clinical and neurophysiological features of FCMTE1 and their association with TTTTA/TTTCA expansion patterns.

METHODS In total, 76 patients from 20 Chinese pedigrees were enrolled. Genetic (TTTTA/TTTCA configuration), clinical (e.g., onset, medication, prognosis, and anticipation) and neurophysiological examination (e.g., electroencephalogram and magnetoencephalography) data were evaluated, and associations between these parameters were analyzed.

RESULTS All patients carried the TTTTA/TTTCA expansion mutation, 19 displayed the (TTTTA)exp(TTTCA)exp (type I) configuration and 1 displayed the (TTTTA)exp (TTTCA)exp(TTTTA)exp (type II) configuration. All patients manifested as progressive tremor, but symptoms of patients carrying type II expansion were more severe. The onset of tremor but not generalized tonic and clonic seizures displayed clinical anticipation between generations of 7 pedigrees, but the pedigree carrying the type II mutation did not show anticipation. Nanopore sequencing showed that the repeats expanded during maternal/offspring transmission (pedigree #7) but shrank during paternal/offspring transmission (pedigree #9). Magnetoencephalographic dipoles were localized in the right frontal lobe near the central sulcus in 4 patients carrying the type I mutation and on the left side in one patient carrying the type II mutation.

SIGNIFICANCE We confirmed the causative roles played by TTTTA/TTTCA repeat expansion in the SAMD12 gene in FCTME1. Both the length and the configuration of the repeats contribute to the clinical and neurophysiological characteristics of the disease.

Keywords: Clinical features, Electrophysiological changes, FCMTE1, Genetic study, TTTTA/TTTCA configurations

Seizure (2021), Vol. 87 (33721773) (5 citations)

Delineation of epileptogenic zones with high frequency magnetic source imaging based on kurtosis and skewness (2021)

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BACKGROUND Neuromagnetic high frequency brain signals (HFBS, > 80 Hz) are a new biomarker for localization of epileptogenic zones (EZs) for pediatric epilepsy.

METHODS Twenty three children with drug-resistant epilepsy and age/sex matched healthy controls were studied with magnetoencephalography (MEG). Epileptic HFBS in 80-250 Hz and 250-600 Hz were quantitatively determined by comparing with normative controls in terms of kurtosis and skewness. Magnetic sources of epileptic HFBS were localized and then compared to clinical EZs determined by invasive recordings and surgical outcomes.

RESULTS Kurtosis and skewness of HFBS were significantly elevated in epilepsy patients compared to healthy controls ($p < 0{,}001$ and $p < 0.0001$, respectively). Sources of elevated MEG signals in comparison to normative data were co-localized to EZs for 22 (22/23, 96 %) patients.

CONCLUSIONS The results indicate, for the first time, that epileptic HFBS can be noninvasively quantified by measuring kurtosis and skewness in MEG data. Magnetic source imaging based on kurtosis and skewness can accurately localize EZs.

SIGNIFICANCE Source imaging of kurtosis and skewness of MEG HFBS provides a novel way for preoperative localization of EZs for epilepsy surgery.

Keywords: Epilepsy, High frequency brain signals, Kurtosis, Magnetic source imaging, Magnetoencephalography, Skewness

Epilepsy research (2021), Vol. 172 (33713889) (0 citations)

Noninvasive Mapping of Ripple Onset Predicts Outcome in Epilepsy Surgery (2021)

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OBJECTIVE Intracranial electroencephalographic (icEEG) studies show that interictal ripples propagate across the brain of children with medically refractory epilepsy (MRE), and the onset of this propagation (ripple onset zone [ROZ]) estimates the epileptogenic zone. It is still unknown whether we can map this propagation noninvasively. The goal of this study is to map ripples (ripple zone [RZ]) and their propagation onset (ROZ) using high-density EEG (HD-EEG) and magnetoencephalography (MEG), and to estimate their prognostic value in pediatric epilepsy surgery.

METHODS We retrospectively analyzed simultaneous HD-EEG and MEG data from 28 children with MRE who underwent icEEG and epilepsy surgery. Using electric and magnetic source imaging, we estimated virtual sensors (VSs) at brain locations that matched the icEEG implantation. We detected ripples on VSs, defined the virtual RZ and virtual ROZ, and estimated their distance from icEEG. We assessed the predictive value of resecting virtual RZ and virtual ROZ for postsurgical outcome. Interictal spike localization on HD-EEG and MEG was also performed and compared with ripples.

RESULTS We mapped ripple propagation in all patients with HD-EEG and in 27 (96%) patients with MEG. The distance from icEEG did not differ between HD-EEG and MEG when mapping the RZ (26-27mm, $p = 0.6$) or ROZ (22-24mm, $p = 0.4$). Resecting the virtual ROZ, but not virtual RZ or the sources of spikes, was associated with good outcome for HD-EEG ($p = 0.016$) and MEG ($p = 0.047$).

INTERPRETATION HD-EEG and MEG can map interictal ripples and their propagation onset (virtual ROZ). Non-invasively mapping the ripple onset may augment epilepsy surgery planning and improve surgical outcome of children with MRE. ANN NEUROL 2021;89:911-925.

Annals of neurology (2021), Vol. 89, No. 5 (33710676) (15 citations)

The Role of Magnetoencephalography and Single-Photon Emission Computed Tomography in Evaluation of Children With Drug-Resistant Epilepsy (2021)

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ABSTRACT Surgery holds the best outcomes for drug-resistant epilepsy in children, making localization of a seizure focus essential. However, there is limited research on the contribution of magnetoencephalography and single-photon emission computed tomography (SPECT) to the presurgical evaluation of lesional and nonlesional pediatric patients. This study proposed to evaluate the concordance of SPECT and magnetoencephalography (MEG) to scalp electroencephalography (EEG) to determine their effective contribution to the presurgical evaluation. On review, MEG and SPECT studies for 28 drug-resistant epilepsy cases were completed at Children's Hospital of Pittsburgh from May 2012 to August 2018. Although not reaching statistical significance, MEG had increased lobar concordance with EEG compared with SPECT (68% vs 46%). MEG or SPECT results effectively provided localization data leading to 6 surgical evaluations and 3 resections with outcomes of Engel class I or II at 12 months. This study suggests MEG and SPECT provide valuable localizing information for presurgical epilepsy evaluation of children with drug-resistant epilepsy.

Keywords: EEG, MEG, SPECT, children, drug-resistant epilepsy, neuroimaging, seizures

Journal of child neurology (2021), Vol. 36, No. 8 (33663250) (0 citations)

Dynamic analysis on simultaneous iEEG-MEG data via hidden Markov model (2021)

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BACKGROUND Intracranial electroencephalography (iEEG) recordings are used for clinical evaluation prior to surgical resection of the focus of epileptic seizures and also provide a window into normal brain function. A major difficulty with interpreting iEEG results at the group level is inconsistent placement of electrodes between subjects making it difficult to select contacts that correspond to the same functional areas. Recent work using time delay embedded hidden Markov model (HMM) applied to magnetoencephalography (MEG) resting data revealed a distinct set of brain states with each state engaging a specific set of cortical regions. Here we use a rare group dataset with simultaneously acquired resting iEEG and MEG to test whether there is correspondence between HMM states and iEEG power changes that would allow classifying iEEG contacts into functional clusters.

METHODS Simultaneous MEG-iEEG recordings were performed at rest on 11 patients with epilepsy whose intracranial electrodes were implanted for pre-surgical evaluation. Pre-processed MEG sensor data was projected to source space. Time delay embedded HMM was then applied to MEG time series. At the same time, iEEG time series were analyzed with time-frequency decomposition to obtain spectral power changes with time. To relate MEG and iEEG results, correlations were computed between HMM probability time courses of state activation and iEEG power time course from the mid contact pair for each electrode in equally spaced frequency bins and presented as correlation spectra for the respective states and iEEG channels. Association of iEEG electrodes with HMM states based on significant correlations was compared to that based on the distance to peaks in subject-specific state topographies.

RESULTS Five HMM states were inferred from MEG. Two of them corresponded to the left and the right temporal activations and had a spectral signature primarily in the theta/alpha frequency band. All the electrodes had significant correlations with at least one of the states ($p < 0.05$ uncorrected) and for 27/50 electrodes these survived within-subject FDR correction ($q < 0.05$). These correlations peaked in the theta/alpha band. There was a highly significant dependence between the association of states and electrodes based on functional correlations and that based on spatial proximity ($p = 5.6e[-6,]\chi[2]$ test for independence). Despite the potentially atypical functional anatomy and physiological abnormalities related to epilepsy, HMM model estimated from the patient group was very similar to that estimated from healthy subjects.

CONCLUSION Epilepsy does not preclude HMM analysis of interictal data. The resulting group functional states are highly similar to those reported for healthy controls. Power changes recorded with iEEG correlate with HMM state time courses in the alpha-theta band and the presence of this correlation can be related to the spatial location of electrode contacts close to the individual peaks of the corresponding state topographies. Thus, the hypothesized relation between iEEG contacts and HMM states exists and HMM could be further explored as a method for identifying comparable iEEG channels across subjects for the purposes of group analysis.

Keywords: Dynamics, Human, Oscillations, Resting state

NeuroImage (2021), Vol. 233 (33662572) (3 citations)

Comparative contribution of magnetoencephalography (MEG) and single-photon emission computed tomography (SPECT) in pre-operative localization for epilepsy surgery: A prospective blinded study (2021)

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PURPOSE The aim of this study was to compare the diagnostic value and accuracy of ictal SPECT and interictal magnetoencephalography (MEG) in localizing the site for surgery in persons with drug resistant epilepsy.

METHOD This was a prospective observational study. Patients expected to undergo epilepsy surgery were enrolled consecutively and the localization results from different imaging modalities were discussed in an epilepsy surgery meet. Odds ratio of good outcome (Engel I) were calculated in patients who underwent surgery in concordance with MEG and SPECT findings. Post-surgical seizure freedom lasting at least 36 months or more was considered the gold standard for determining the diagnostic output of SPECT and MEG.

RESULTS MEG and SPECT were performed in 101 and 57 patients respectively. In 45 patients SPECT could not be done due to delay in injection or technical factors. The accuracy of MEG and SPECT in localizing the epileptogenic zone was found to be 74.26 % and 78.57 % respectively. The diagnostic odds ratio for Engel I surgical outcome was reported as 2.43 and 5.0 for MEG and SPECT respectively. The diagnostic odds ratio for MEG in whom SPECT was non-informative was found to be 6.57 [95 % CI 1.1, 39.24], although it was not significantly associated with good surgical outcome. MEG was useful in indicating sites for SEEG implantation.

CONCLUSION SPECT was found to be non-informative for most patients, but reported better diagnostic output than MEG. MEG may be a useful alternative for patients in whom SPECT cannot be done or was non-localizing.

Keywords: Epilepsy, Epilepsy surgery, Magnetoencephalography (MEG), Neuroimaging, Single-photon emission computed tomography (SPECT)

Seizure (2021), Vol. 86 (33647809) (6 citations)

Interictal spike localization for epilepsy surgery using magnetoencephalography beamforming (2021)

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OBJECTIVE Magnetoencephalography (MEG) kurtosis beamforming is an automated localization method for focal epilepsy. Visual examination of virtual sensors, which are source activities reconstructed by beamforming, can improve performance but can be time-consuming for neurophysiologists. We propose a framework to automate the method and evaluate its effectiveness against surgical resections and outcomes.

METHODS We retrospectively analyzed MEG recordings of 13 epilepsy surgery patients who had one-year minimum post-operative follow-up. Kurtosis beamforming was applied and manual inspection was confined to morphological clusters. The region with the Maximum Interictal Spike Frequency (MISF) was validated against prospectively modelled sLORETA solutions and surgical resections linked to outcome.

RESULTS Our approach localized spikes in 12 out of 13 patients. In eight patients with Engel I surgical outcomes, beamforming MISF regions were concordant with surgical resection at overlap level for five patients and at lobar level for three patients. The MISF regions localized to spike onset and propagation modelled by sLORETA in two and six patients, respectively.

CONCLUSIONS Automated beamforming using MEG can predict postoperative seizure freedom at the lobar level but tends to localize propagated MEG spikes.

SIGNIFICANCE MEG beamforming may contribute to non-invasive procedures to predict surgical outcome for patients with drug-refractory focal epilepsy.

Keywords: Beamforming, Epilepsy surgery, Interictal spikes, MEG, Source localization

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2021), Vol. 132, No. 4 (33636608) (2 citations)

A computational biomarker of juvenile myoclonic epilepsy from resting-state MEG (2021)

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OBJECTIVE For people with idiopathic generalized epilepsy, functional networks derived from their resting-state scalp electrophysiological recordings have shown an inherent higher propensity to generate seizures than those from healthy controls when assessed using the concept of brain network ictogenicity (BNI). Herein we tested whether the BNI framework is applicable to resting-state magnetoencephalography (MEG) from people with juvenile myoclonic epilepsy (JME).

METHODS The BNI framework consists in deriving a functional network from apparently normal brain activity, placing a mathematical model of ictogenicity into the network and then computing how often such net-

work generates seizures in silico. We considered data from 26 people with JME and 26 healthy controls.

RESULTS We found that resting-state MEG functional networks from people with JME are characterized by a higher propensity to generate seizures (i.e., higher BNI) than those from healthy controls. We found a classification accuracy of 73%.

CONCLUSIONS The BNI framework is applicable to MEG and was capable of differentiating people with epilepsy from healthy controls.

SIGNIFICANCE The BNI framework may be applied to resting-state MEG to aid in epilepsy diagnosis.

Keywords: Biomarker, Epilepsy diagnosis, Functional connectivity, Juvenile myoclonic epilepsy, MEG, Phenomenological model

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2021), Vol. 132, No. 4 (33636607) (4 citations)

Voxel-based morphometric MRI post-processing and PET/MRI co-registration reveal subtle abnormalities in cingulate epilepsy (2021)

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OBJECTIVE Diagnostic challenges exist in the presurgical evaluation of patients with magnetic resonance imaging (MRI) negative cingulate epilepsy (CE) because of the heterogeneity in clinical semiology and lack of localizing findings on scalp electroencephalographic (EEG) recordings. We aimed to examine the neuroimaging characteristics in a consecutive cohort of patients with MRI-negative CE with a focus on two image post-processing methods, including the MRI post-processing morphometric analysis program (MAP) and [18] F-fluorodeoxyglucose-positron emission tomography-MRI (PET/MRI) co-registration.

METHODS Included in this retrospective study were patients with MRI-negative CE who met the following criteria: negative on preoperative MRI, invasive EEG (iEEG) confirmed cingulate gyrus-onset seizures, surgical resection of the cingulate gyrus with/without adjacent cortex, and seizure-free for more than 12 months. MAP and PET/MRI co-registration were performed and investigated by comparison to ictal intracranial EEG findings. Other characteristics obtained from scalp EEG, magnetoencephalography (MEG), iEEG, and pathological study were also reported.

RESULTS Ten patients were included, of which eight were diagnosed with anterior CE, one with middle CE, and one with posterior CE. The semiology included fear, embarrassment, vocalization, ictal pouting, asymmetric tonic posture, hypermotor, and automatism. Scalp EEG revealed unilateral or bilateral frontal-temporal onset. MEG localized the dipoles correctly in one patient (1/10). MAP detected subtle abnormalities in regions concordant with iEEG onset in seven patients (7/10) while PET/MRI co-registration revealed focal concordant hypometabolism in five patients (5/10). Combining MAP with PET/MRI co-registration improved the detection rate to 90 % in this cohort. The pathology was focal cortical dysplasia (FCD), including FCD type IIA in three, type IIB in three, and type I in four.

CONCLUSION MAP and PET/MRI co-registration show promising results in identifying subtle FCD abnormalities in CE with negative results on conventional MRI, which can be otherwise challenging. More importantly, a combination of MRI post-processing and PET/MRI co-registration can greatly improve the identification of epileptic abnormalities, which can be used as surgical target. MAP and PET/MRI co-registration should be incorporated into the routine presurgical evaluation.

Keywords: Cingulate epilepsy, Focal cortical dysplasia, Invasive electroencephalography, Magnetic resonance imaging, Magnetoencephalography, Morphometric analysis program, PET/MRI co-registration

Epilepsy research (2021), Vol. 171 (33610065) (4 citations)

Advantages of magnetoencephalography, neuronavigation and intraoperative MRI in epilepsy surgery re-operations (2021)

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ABSTRACT Objective: Management of patients after failed epilepsy surgery is still challenging. Advanced diagnostic and intraoperative tools including magnetoencephalography (MEG) as well as neuronavigation and intraoperative magnetic resonance imaging (iopMRI) may contribute to a better postoperative seizure outcome in this patient group.Methods: We retrospectively analyzed consecutive patients after reoperation of failed epilepsy surgery for medically refractory epilepsy at the University of Erlangen between 1988 and 2017. Inclusion criteria for patients were available MEG, neuronavigation and iopMRI data. The Engel scale was used to categorize seizure outcome.Results: We report on 27 consecutive patients (13 female/14 male mean age at first surgery 29.4 years) who had operative revision of the first resection after failed epilepsy surgery. An improved seizure outcome postoperatively was observed in 78% of patients ($p < 0.001$) with 55% seizure free (Engel I) patients after a mean follow-up time of 4.9 years. In detail, 80% of lesional cases were seizure free compared to 59% of MRI negative patients. Localizing MEG spike activity in the vicinity of the first resection cavity was present in 12 of 27 patients (44%) corresponding to 83% (10/12) of MEG localizing spike patients having advanced seizure outcome after operative revision.Conclusion: Re-operation after failed surgery in refractory epilepsy may lead to a better seizure outcome in the majority of patients. Preoperative MEG may support the decision for surgery and may facilitate targeting epileptogenic tissue for re-resection by employing navigation and iopMR imaging.

Keywords: Failed epilepsy surgery, MEG, intraoperative MR imaging, neuronavigation, reoperation, seizure outcome

Neurological research (2021), Vol. 43, No. 6 (33402062) (2 citations)

Succinic Semialdehyde Dehydrogenase Deficiency: Review of the Natural History Study (2021)

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OBJECTIVE The SSADHD Natural History Study was initiated in 2019 to define the natural course and identify biomarkers correlating with severity.

METHODS The study is conducted by 4 institutions: BCH (US clinical), WSU (bioanalytical core), USF (biostatistical core), and Heidelberg (iNTD), with support from the family advocacy group (SSADH Association).

Recruitment goals were to study 20 patients on-site at BCH, 10 with iNTD, and 25 as a standard-of care cohort.

RESULTS At this half-way point of this longitudinal study, 28 subjects have been recruited (57% female, mean 9 years, range 18 months-40 years). Epilepsy is present in half and increases in incidence and severity, as do psychiatric symptoms, in adolescence and adulthood. The average Full Scale IQ (FSIQ) was 53 (Verbal score of 56, Non Verbal score of 49), and half scored as having ASD. Although there was no correlation between gene variant and phenotypic severity, there were extreme cases of lowest functioning in one individual and highest in another that may have genotype-phenotype correlation. The most common EEG finding was mild background slowing with rare epileptiform activity, whereas high-density EEG and magnetoencephalography showed reduction in the gamma frequency band consistent with GABAergic dysfunction. MR spectroscopy showed elevations in the GABA/NAA ratio in all regions studied with no crossover between subjects and controls.

CONCLUSIONS The SSADH Natural History Study is providing a unique opportunity to study the complex pathophysiology longitudinally and derive electrophysiologic, neuroimaging, and laboratory data for correlation and to serve as biomarkers for clinical trials and prognostic assessments in this ultra-rare inherited disorder of GABA metabolism.

Keywords: epilepsy, genetics, inborn errors of metabolism, intellectual disability, metabolism, neuroimaging

Journal of child neurology (2021), Vol. 36, No. 13-14 (33393837) (4 citations)

The utility of arterial spin labeling in the presurgical evaluation of poorly defined focal epilepsy in children (2020)

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OBJECTIVE The authors sought to assess the utility of arterial spin labeling (ASL) perfusion 3T-MRI for the presurgical evaluation of poorly defined focal epilepsy in pediatric patients.

METHODS Pseudocontinuous ASL perfusion 3T-MRI was performed in 25 consecutive children with poorly defined focal epilepsy. ASL perfusion abnormalities were detected qualitatively by visual inspection and quantitatively by calculating asymmetry index (AI) maps and significant z-score cluster maps based on successfully operated cases. ASL results were prospectively compared to scalp EEG, structural 3T-MRI, FDG-PET, ictal/interictal SPECT, magnetoencephalography (MEG), and intracranial recording results, as well as the final surgically proven epileptogenic zone (EZ) in operated patients who had at least 1 year of good (Engel class I/II) seizure outcome and positive histopathology results.

RESULTS Qualitative ASL perfusion abnormalities were found in 17/25 cases (68%), specifically in 17/20 MRI-positive cases (85.0%) and in none of the 5 MRI-negative cases. ASL was concordant with localizing scalp EEG findings in 66.7%, structural 3T-MRI in 90%, FDG-PET in 75%, ictal/interictal SPECT in 62.5%, and MEG in 75% of cases, and with intracranial recording results in 40% of cases. Eleven patients underwent surgery; in all 11 cases the EZ was surgically proven by positive histopathology results and the patient having at least 1 year of good seizure outcome. ASL results were concordant with this final surgically proven EZ in 10/11 cases (sensitivity 91%, specificity 50%). All 10 ASL-positive patients who underwent surgery had positive surgical pathology results and good long-term postsurgical seizure outcome at a mean follow-up of 39 months. Retrospective quantitative analysis based on significant z-score clusters found 1 true-positive result that was missed by qualitative analysis and 3 additional false-positive results (sensitivity 100%, specificity 23%).

CONCLUSIONS ASL supports the hypothesis regarding the EZ in poorly defined focal epilepsy cases in children. Due to its convenience and noninvasive nature, the authors recommend that ASL be added routinely to the presurgical MRI evaluation of epilepsy. Future optimized quantitative methods may improve the diagnostic yield of this technique.

Keywords: epilepsy surgery, perfusion MRI, presurgical evaluation

Journal of neurosurgery. Pediatrics (2020), Vol. 27, No. 3 (33361483) (8 citations)

Is beta band desynchronization related to skin conductance biofeedback effectiveness in drug resistant focal epilepsy? (2021)

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ABSTRACT Skin Conductance Biofeedback (SCB) is a non-invasive behavioral treatment for epilepsy based on modulation of Galvanic Skin Response (GSR). We evaluated changes in functional connectivity occurring after SCB. Six patients with drug-resistant temporal lobe epilepsy underwent monthly SCB sessions. For each patient, 10 min of resting-state magnetoencephalographic (MEG) recording were acquired before and after the first and the last SCB session. For each recording we computed the mean weighted phase lag index (WPLI) across all pair of MEG sensors. After SCB, two patients had consistent reduction of seizure frequency (>50 %). Connectivity analysis revealed a decrease of WPLI-beta band in the two responders and an increase of WPLI-alpha connectivity in all patients regardless of the clinical effect. Results suggest that reduction of WPLI-beta-low connectivity is related to the clinical response after SCB.

Keywords: Biofeedback, Connectivity, Epilepsy, Magnetoencephalography, Phase-Lag-Index

Epilepsy research (2021), Vol. 169 (33360538) (3 citations)

Reinterpretation of magnetic resonance imaging findings with magnetoencephalography can improve the accuracy of detecting epileptogenic cortical lesions (2021)

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OBJECTIVE This study examined whether the application of magnetoencephalography (MEG) to interpret

magnetic resonance imaging (MRI) findings can aid the diagnosis of intractable epilepsy caused by organic brain lesions.

METHODS This study included 51 patients with epilepsy who had MEG clusters but whose initial MRI findings were interpreted as being negative for organic lesions. Three board-certified radiologists reinterpreted the MRI findings, utilizing the MEG findings as a guide. The degree to which the reinterpretation of the imaging results identified an organic lesion was rated on a 5-point scale.

RESULTS Reinterpretation of the MRI data with MEG guidance helped detect an abnormality by at least one radiologist in 18 of the 51 patients (35.2%) with symptomatic localization-related epilepsy. A surgery was performed in 7 of the 51 patients, and histopathological analysis results identified focal cortical dysplasia in 5 patients (Ia: 1, IIa: 2, unknown: 2), hippocampal sclerosis in 1 patient, and dysplastic neurons/gliosis in 1 patient.

CONCLUSIONS The results of this study highlight the potential diagnostic applications of MEG to detect organic epileptogenic lesions, particularly when radiological visualization is difficult with MRI alone.

Keywords: Epilepsy, Epileptogenic zone, Focal cortical dysplasia, Magnetic resonance imaging, Magnetoencephalography

Epilepsy & behavior: E&B (2021), Vol. 114, No. Pt A (33323336) (1 citation)

Seizure detection and epileptogenic zone localisation on heavily skewed MEG data using RUSBoost machine learning technique (2022)

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ABSTRACT Background: Epilepsy is a neurological disorder which is characterised by recurrent and involuntary seizures. Magnetoencephalography (MEG) is clinically used as a presurgical tool in locating the epileptogenic zone by localising either interictal epileptic discharges (IEDs) or ictal activities. The localisation of ictal onset provides reliable and more accurate seizure onset zones rather than localising the IEDs. Ictals or seizures are presently detected during MEG analysis by manually inspecting the recorded data. This is laborious when the duration of recordings is longer. Methods: We propose a novel method which uses statistical features such as short-time permutation entropy (STPE), gradient of STPE (GSTPE), short-time energy (STE) and short-time mean (STM) extracted from the ictal and interictal MEG data of drug resistant epilepsy patients group. Since the data is heavily skewed, the RUSBoost algorithm with k-fold cross-validation is used to classify the data into ictal and interictal by using the four feature vectors. This method is further used for localising the epileptogenic region using region-specific classifications by means of the RUSBoost algorithm. Results: The accuracy obtained for seizure detection is 93.4%. The specificity and sensitivity for the same are 93%. The localisation accuracies for each lobe are in the range of 88.1-99.1%. Discussion: Through this ictus detection method, the current scenario of laborious inspection of the ictal MEG can be reduced. The proposed system, thus, can be implemented in real-time as a better and more efficient method for seizure detection and further it can prove to be highly beneficial for patients and health-care professionals during real-time MEG recording. Furthermore, the identification of the epileptogenic lobe can provide clinicians with useful insights, and a pre-cursor for source localisation.

Keywords: EEG, MEG, RUSBoost, artificial neural networks, classification, epileptogenic zone, ictal, inter-ictal, machine learning, permutation entropy, seizure detection

The International journal of neuroscience (2022), Vol. 132, No. 10 (33272081) (1 citation)

P300 in mesial temporal lobe epilepsy and its correlation with cognition - A MEG based prospective case-control study (2021)

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PURPOSE To assess the role of P300 in patients with temporal lobe epilepsy (TLE) with unilateral hippocampal sclerosis (HS) using magnetoencephalography (MEG) based auditory and visual oddball tasks, and to assess its correlation with neuropsychological tests.

METHODS Thirty-patients (M:F-17:13, onset-11.77 ± 8.75 years, duration-16.10 ± 9.61 years) with TLE-HS (Left:15, Right:15) and fifteen-healthy age, gender and years of education matched controls (M:F-10:5, age-28.13 ± 4.76 years) underwent auditory and visual oddball tasks in MEG and cognition assessment using Indian Council of Medical Research (ICMR)-cognitive test battery. Independent component analysis (ICA) was applied to the magnetic evoked field responses for the detection of the P300 component. Source localization of P300 was performed with Classical LORETA Analysis Recursively Applied (CLARA). The latency and amplitude of P300 were estimated and subsequently correlated with cognitive scores.

RESULTS The visual P300 amplitude in the TLE group was lower when compared to the control group. In subgroup comparison (controls vs. right HS vs. left HS), visual P300 amplitudes were lower in the right HS group compared to both left HS and control groups (p-value = 0.014). On the other hand, no significant difference for auditory P300 latency or amplitude was noted between patients and controls as well as between subgroups. A negative correlation found between the MEG visual P300 amplitude and Indian Trial Making Test (TMT)-B duration in the patient group.

CONCLUSION Patients with TLE-HS have decreased visual-P300 amplitude. A significant correlation found between visual P300 amplitude and cognitive tests of visuospatial attention and working memory. Overall, MEG based visual P300 amplitude can be further explored with large sample size studies to establish as a complementary objective test for cognitive assessment in TLE.

Keywords: CLARA, Event related field, ICA, Magnetoencephalography, P300, Temporal lobe epilepsy

Epilepsy & behavior: E&B (2021), Vol. 114, No. Pt A (33248942) (3 citations)

Contributions of electrophysiology for identifying cortical language systems in patients with epilepsy (2020)

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ABSTRACT A crucial element of the surgical treatment of medically refractory epilepsy is to delineate cortical areas that must be spared in order to avoid clinically relevant neurological and neuropsychological deficits postoperatively. For each patient, this typically necessitates determining the language lateraliza-

tion between hemispheres and language localization within hemisphere. Understanding cortical language systems is complicated by two primary challenges: the extent of the neural tissue involved and the substantial variability across individuals, especially in pathological populations. We review the contributions made through the study of electrophysiological activity to address these challenges. These contributions are based on the techniques of magnetoencephalography (MEG), intracerebral recordings, electrical-cortical stimulation (ECS), and the electrovideo analyses of seizures and their semiology. We highlight why no single modality alone is adequate to identify cortical language systems and suggest avenues for improving current practice.

Keywords: Aphasia, Electrical–cortical stimulation, Electrocorticography, Magnetoencephalography, Seizure semiology, Stereotactic electroencephalography

Epilepsy & behavior: E&B (2020), Vol. 112 (33181892) (5 citations)

Utilization of MEG Among the US Epilepsy Centers: A Survey-Based Appraisal (2020)

Bagić, Anto I; Burgess, Richard C

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PURPOSE The purported underutilization of magnetoencephalography (MEG) among the USA epilepsy centers has never been studied, and any evidence-based understanding of its magnitude is lacking.

METHODS Two hundred twenty-five National Association of Epilepsy Centers centers (2016) were invited to participate anonymously in a 13-question web-based survey of clinical practice focused on MEG use.

RESULTS On average, centers (N = 70; 61 of which were level 4) reported <6 epileptologists, >7 dedicated epilepsy monitoring unit beds, 206 phase 1 studies, 15 phase 2 studies, 10 direct resections, and 9 indirect resections; 27% owned MEG. On average, 11.2 MEGs per year were ordered for epilepsy localization and 7.6 for any presurgical mapping modalities. Wada test aka the intracarotid sodium amobarbital procedure (ISAP) (43%) and functional MRI (29%) were preferred over MEG (4%) for language mapping. The number of epileptologists and the number of epilepsy monitoring unit beds correlated positively with the most clinical volumes. The centers who own a MEG had surgical volumes significantly higher than those without. The number and complexity of patients as well as the proximity of a MEG were perceived as significant contributors/obstacles to increased MEG use.

CONCLUSIONS Only the centers with larger surgical volumes incorporate MEG regularly in presurgical evaluation of patients with drug-resistant epilepsy. A reversal of the pervasive underutilization of epilepsy surgery can benefit from MEG, but this requires a sustained concerted promotion by the epilepsy and MEG communities.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165233) (18 citations)

Clinical Magnetoencephalography Practice in the United States Ten Years Later: A Survey-Based Reappraisal (2020)

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PURPOSE Broader utilization of magnetoencephalography (MEG) and optimization of clinical practice remain strategic goals of the American Clinical Magnetoencephalography Society. Despite the implementation of the first MEG Clinical Practice Guidelines, clinical adoption has been less than expected, prompting a reassessment.

METHODS Twenty-five clinical MEG centers were invited to participate anonymously in a survey of clinical practice.

RESULTS Centers (N = 18) mostly operated within an academic medical center (10/18), were owned by the "hospital" (10/18), associated with a level 4 National Association of Epilepsy center (15/18), and directed by neurologists (10/18). A total of 873 (median 59) epilepsy studies, 1,179 evoked fields (of all types), and 1,607 (median 30) research MEG studies were reported. Fourteen of 17 centers serve children (median 35%), but only 5 of 14 sedate children for MEG. All (N = 14) centers record EEG simultaneous with MEG, and 57% used dipole source localization. The median reporting time for epilepsy studies was 12 and 10 days for presurgical mapping studies. Most (12/14) were favorable toward the Clinical Practice Guidelines and "formalized certification" but were against mandating the latter.

CONCLUSIONS A plateau in MEG volumes suggests that MEG has not become a part of the standard of care, and correspondingly, the Clinical Practice Guidelines appeared to have had little impact on clinical practice. The American Clinical Magnetoencephalography Society must continue to engage magnetoencephalographers, potential referrers, and vendors.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165232) (11 citations)

Language Mapping With Magnetoencephalography: An Update on the Current State of Clinical Research and Practice With Considerations for Clinical Practice Guidelines (2020)

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ABSTRACT Numerous studies have shown that language processing is not limited to a few brain areas. Visual or auditory stimuli activate corresponding cortical areas, then memory identifies the word or image, Wernicke's and Broca's areas support the processing for either reading/listening or speaking and many areas of the brain are recruited. Determining how a normal person processes language helps clinicians and scientist to understand how brain pathologies such as tumor or stroke can affect changes in language processing. Patients with epilepsy may develop atypical language organization. Over time, the chronic nature of epileptic activity, or changes from a tumor or stroke, can result in a shift of language processing area from the left to the right hemisphere, or re-routing of language pathways from traditional to non-traditional areas within the dominant left hemisphere. It is important to determine where these language areas are prior to brain surgery. MEG evoked responses reflecting cerebral activation of receptive and expressive language processing can be localized using several different techniques: Single equivalent current dipole, current distribution techniques or beamformer techniques. Over the past 20 years there have been at least 25 validated MEG studies that indicate MEG can be used to determine the dominant hemisphere for language processing. The use of MEG neuroimaging techniques is needed to reliably predict altered language networks in patients and to provide identification of language eloquent cortices for localization and lateralization necessary for clinical care.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165228) (12 citations)

MEG Reporting (2020)

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ABSTRACT The report generated by the magnetoencephalographer's interpretation of the patient's mag-

netoencephalography examination is the magnetoencephalography laboratory's most important product and is a representation of the quality of the laboratory and the clinical acumen of the personnel. A magnetoencephalography report is not meant to enumerate all the technical details that went into the test nor to fulfill some imagined requirements of the electronic health record. It is meant to clearly and concisely answer the clinical question posed by the referring doctor and to convey the key findings that may inform the next step in the patient's care. The graphical component of a magnetoencephalography report is ordinarily the most welcomed by the referring doctor. Much of the text of the report may be glossed over, so the illustrations must be sufficiently annotated to provide clear and unambiguous findings. The particular images chosen for the report will be a function of the analysis software but should be selected and edited for maximum clarity. There should be a composite pictorial summary slide at the beginning or at the end of the report, which accurately conveys the gist of the report. Along with representative source localizations, reports should contain examples of the simultaneously recorded EEG that enable the referring physician to determine whether epileptic discharges occurred and whether they are consistent with the patient's previously recorded spikes. Information and images (e.g., statistics, magnetic field patterns) that provide convincing evidence of the validity of the source location should also be included.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165227) (3 citations)

The Value of Source Localization for Clinical Magnetoencephalography: Beyond the Equivalent Current Dipole (2020)

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ABSTRACT Source localization for clinical magnetoencephalography recordings is challenging, and many methods have been developed to solve this inverse problem. The most well-studied and validated tool for localization of the epileptogenic zone is the equivalent current dipole. However, it is often difficult to summarize the richness of the magnetoencephalography data with one or a few point sources. A variety of source localization algorithms have been developed to more fully explain the complexity of clinical magnetoencephalography data used to define the epileptogenic network. In this review, various clinically available source localization methods are described and their individual strengths and limitations are discussed.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165226) (8 citations)

Normal Variants in Magnetoencephalography (2020)

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ABSTRACT Normal variants, although not occurring frequently, may appear similar to epileptic activity. Misinterpretation may lead to false diagnoses. In the context of presurgical evaluation, normal variants may lead to mislocalizations with severe impact on the viability and success of surgical therapy. While the different variants are well known in EEG, little has been published in regard to their appearance in magnetoencephalography. Furthermore, there are some magnetoencephalography normal variants that have no counterparts in EEG. This article reviews benign epileptiform variants and provides examples in EEG and magnetoencephalography. In addition, the potential of oscillatory configurations in different frequency bands to appear as epileptic activity is discussed.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165225) (2 citations)

The 10 Common Evidence-Supported Indications for MEG in Epilepsy Surgery: An Illustrated Compendium (2020)

Bagić, Anto I; Funke, Michael E; Kirsch, Heidi E; Tenney, Jeffrey R; Zillgitt, Andrew J; Burgess, Richard C

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ABSTRACT Unfamiliarity with the indications for and benefits of magnetoencephalography (MEG) persists, even in the epilepsy community, and hinders its acceptance to clinical practice, despite the evidence. The wide treatment gap for patients with drug-resistant epilepsy and immense underutilization of epilepsy surgery had similar effects. Thus, educating referring physicians (epileptologists, neurologists, and neurosurgeons) both about the value of epilepsy surgery and about the potential benefits of MEG can achieve synergy and greatly improve the process of selecting surgical candidates. As a practical step toward a comprehensive educational process to benefit potential MEG users, current MEG referrers, and newcomers to MEG, the authors have elected to provide an illustrated guide to 10 everyday situations where MEG can help in the evaluation of people with drug-resistant epilepsy. They are as follows: (1) lacking or imprecise hypothesis regarding a seizure onset; (2) negative MRI with a mesial temporal onset suspected; (3) multiple lesions on MRI; (4) large lesion on MRI; (5) diagnostic or therapeutic reoperation; (6) ambiguous EEG findings suggestive of "bilateral" or "generalized" pattern; (7) intrasylvian onset suspected; (8) interhemispheric onset suspected; (9) insular onset suspected; and (10) negative (i.e., spikeless) EEG. Only their practical implementation and furtherance of personal and collective education will lead to the potentially impactful synergy of the two-MEG and epilepsy surgery. Thus, while fulfilling our mission as physicians, we must not forget that ignoring the wealth of evidence about the vast underutilization of epilepsy surgery - and about the usefulness and value of MEG in selecting surgical candidates - is far from benign neglect.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 6 (33165222) (7 citations)

Redefining the role of Magnetoencephalography in refractory epilepsy (2020)

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ABSTRACT Magnetoencephalography (MEG) possesses a number of features, including excellent spatiotemporal resolution, that lend itself to the functional imaging of epileptic activity. However its current use is restricted to specific scenarios, namely in the diagnosis refractory focal epilepsies where electroencephalography (EEG) has been inconclusive. This review highlights the recent progress of MEG within epilepsy, including advances in the technique itself such as simultaneous EEG/MEG and intracranial EEG/MEG recording and room temperature MEG recording using optically pumped magnetom-

eters, as well as improved post processing of the data during interictal and ictal activity for accurate source localisation of the epileptogenic focus. These advances should broaden the scope of MEG as an important part of epilepsy diagnostics in the future.

Keywords: OPMs, electroencephalograph, magnetoencephalography, source localisation

Seizure (2020), Vol. 83 (33096459) (0 citations)

Bridging the gap between analytical methods and their clinical interpretation (2020)

Kaur, Kirandeep; Chandra, Poodepedi Sarat; Samala, Raghu; Agrawal, Mohit; Doddamani, Ramesh; Ramanujam, Bhargavi; Singh, Gaurav; Tripathi, Manjari

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Epilepsia (2020), Vol. 61, No. 11 (33063844) (0 citations)

Multidimensional analytical methods and their clinical interpretation (2020)

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Epilepsia (2020), Vol. 61, No. 11 (33063843) (0 citations)

Electromagnetic evidence that benign epileptiform transients of sleep are traveling, rotating hippocampal spikes (2020)

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OBJECTIVE Benign epileptiform transients of sleep (BETS) have a unique voltage topography and a posteriorly propagating, inferiorly rotating diphasic EEG pattern. The source generators of BETS have not been definitively identified. We aimed to clarify the cerebral localization of BETS using MEG and electromagnetic source imaging (EMSI).

METHODS We analyzed BETS recorded with simultaneous MEG and EEG in four patients with epilepsy. Magnetic source imaging (MSI) and EMSI using equivalent current, single moving and rotating dipole inverse models was performed on averaged BETS potentials. MEG beamforming was performed in one case with abundant BETS.

RESULTS MSI and EMSI revealed hippocampal dipole source maxima in all cases, with current flow direction rotating from inferomedial to superomedial or superolateral between the first and second BETS peaks. Moving dipole analyses revealed spatiotemporal propagation along the anterior-posterior hippocampal axis and concomitant electromagnetic field rotation. Beamformer source reconstruction revealed an identical hippocampal localization.

CONCLUSIONS Converging evidence from different electromagnetic inverse modeling methods indicates that BETS are traveling, rotating hippocampal spikes, whose diphasic waveform is due to back and forth propagation along the anterior-posterior axis of the hippocampus.

SIGNIFICANCE The hippocampal localization and longitudinal, rotating propagation pattern of BETS raises the possibility of a sleep-related functional role for these hippocampal spikes.

Keywords: BETS, EEG, Hippocampus, MEG, Magnetic source imaging (MSI), Small sharp spikes (SSS)

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 12 (32988727) (6 citations)

Secondary epileptogenesis on gradient magnetic-field topography correlates with seizure outcomes after vagus nerve stimulation (2020)

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OBJECTIVE To determine the correlation between secondary unilateral or bilateral spreading on gradient magnetic-field topography (GMFT) before and after vagus nerve stimulation (VNS), and postoperative seizure outcomes.

METHODS We analyzed pre- and post-VNS magnetoencephalography (MEG) in 15 patients with VNS implants. We applied McHugh classification to evaluate seizure outcomes. GMFT visualized the spatiotemporal spread of the gradient magnetic field from MEG (>300 fT/cm) before and after the spike peak. We compared the proportion of bilaterally spreading (PBS) MEG spikes and seizure outcomes. We also compared the interhemispheric time difference (ITD) between patients with and without corpus callosotomy.

RESULTS We allocated patients with favorable seizure outcomes of class I and II to group A (9 patients) and poor outcomes of class III-V to group B (6 patients). The number of post-VNS MEG spikes was significantly reduced compared to pre-VNS MEG spikes in group A, but not in group B. Group A showed significantly higher preoperative PBS than group B. Postoperative ITD significantly decreased in 5 patients who underwent corpus callosotomy compared to 10 patients without.

CONCLUSION GMFT can detect the inter- and intra-hemispheric spreading of spikes with high spatiotemporal resolution on the brain surface. Frequent interictal MEG spikes propagating bilaterally on GMFT may reflect a favorable seizure outcome after VNS. GMFT can identify dependent secondary epileptogenic spikes responding to VNS, which may be used to control generalized seizures in a subset of patients with pharmacoresistant epilepsy.

Keywords: Bilateral spreading, Dependent spikes, Gradient magnetic field topography, Magnetoencephalography, Secondary epileptogenesis, Vagus nerve stimulation

Epilepsy research (2020), Vol. 167 (32987243) (2 citations)

Awake state-specific suppression of primary somatosensory evoked response correlated with duration of temporal lobe epilepsy (2020)

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ABSTRACT Epilepsy is a network disease. The primary somatosensory cortex (S1) is usually considered to be intact, but could be subclinically disturbed based on abnormal functional connectivity in patients with temporal lobe epilepsy (TLE). We aimed to investigate if the S1 of TLE is abnormally modulated. Somatosensory

evoked magnetic fields (SEFs) evoked by median nerve stimulation were recorded in each hemisphere of 15 TLE patients and 28 normal subjects. All responses were separately averaged in the awake state and light sleep using background magnetoencephalography. Latency and strength of the equivalent current dipole (ECD) was compared between the groups for the first (M1) and second peaks. Latencies showed no significant differences between the groups in either wakefulness or light sleep. ECD strengths were significantly lower in TLE patients than in controls only during wakefulness. The reduction of M1 ECD strength in the awake state is significantly correlated with duration of epilepsy. SEFs of TLE patients showed pure ECD strength reduction without latency delay. The phenomenon occurred exclusively during wakefulness, suggesting that a wakefulness-specific modulator of S1 is abnormal in TLE. Repetitive seizures may gradually insult the modulator of S1 distant from the epileptogenic network.

Scientific reports (2020), Vol. 10, No. 1 (32985579) (1 citation)

The relationship between epilepsy and cognitive function in benign childhood epilepsy with centrotemporal spikes (2020)

Li, Yihan; Sun, Yulei; Zhang, Tingting; Shi, Qi; Sun, Jintao; Xiang, Jing; Chen, Qiqi; Hu, Zheng; Wang, Xiaoshan

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INTRODUCTION This study was aimed to explore the relationship between neural network changes in newly diagnosed children with Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS) and cognitive impairment.

METHODS Children's cognition was evaluated using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). Magnetoencephalographic (MEG) data of 18 healthy children and 22 BECTS patients were recorded in order to construct a functional connectivity (FC) network, which was quantified by graph theory (GT).

RESULTS The mean age of the control group was 7.94 ± 1.89 years, and the mean age of BECTS patients was 8.14 ± 1.73 years. Our results show that the WISC-IV index scores in the BECTS group were significantly lower than those in the control group. Besides, the FC network pattern of BECTS patients changed significantly in the 12-30, 30-80, and 250-500 Hz frequency band. The local functional connections between posterior cingulate cortex (PCC) and frontal lobe varied significantly in 12-30, 80-250, and 250-500 Hz. Our GT analysis shows that the connection strength of BECTS patients increases significantly in the 12-30 Hz frequency band, the path length decreases significantly in the 12-30 Hz and 30-80 Hz frequency bands, with the clustering coefficient decreasing significantly in the 12-30 Hz, 30-80 Hz, and 250-500 Hz frequency bands. Correlation analysis showed that the full-scale IQ (FSIQ) was positively correlated with the 12-30 Hz clustering coefficient, verbal comprehension index (VCI) was positively correlated with the 250-500 Hz clustering coefficient, perceptual reasoning index (PRI) was positively correlated with the 12-30 Hz clustering coefficient, and perceptual reasoning index (PSI) was negatively correlated with the 12-30 Hz path length.

CONCLUSION There is a trend of cognitive impairment in patients with early BECTS. This trend of cognitive impairment in early BECTS children may be related to the changes in the FC network pattern.

Keywords: benign childhood epilepsy with centrotemporal spikes, functional connectivity, graph theory, magnetoencephalography, multi-frequency, neural network

Brain and behavior (2020), Vol. 10, No. 12 (32959999) (9 citations)

Recurrence quantification analysis of dynamic brain networks (2021)

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ABSTRACT Evidence suggests that brain network dynamics are a key determinant of brain function and dysfunction. Here we propose a new framework to assess the dynamics of brain networks based on recurrence analysis. Our framework uses recurrence plots and recurrence quantification analysis to characterize dynamic networks. For resting-state magnetoencephalographic dynamic functional networks (dFNs), we have found that functional networks recur more quickly in people with epilepsy than in healthy controls. This suggests that recurrence of dFNs may be used as a biomarker of epilepsy. For stereo electroencephalography data, we have found that dFNs involved in epileptic seizures emerge before seizure onset, and recurrence analysis allows us to detect seizures. We further observe distinct dFNs before and after seizures, which may inform neurostimulation strategies to prevent seizures. Our framework can also be used for understanding dFNs in healthy brain function and in other neurological disorders besides epilepsy.

Keywords: MEG, epilepsy, functional network, stereo EEG

The European journal of neuroscience (2021), Vol. 53, No. 4 (32888203) (4 citations)

The relationship between neuromagnetic activity and cognitive function in benign childhood epilepsy with centrotemporal spikes (2020)

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PURPOSE Our aim was to explore the pathophysiological mechanism of cognitive function changes in early untreated children with benign childhood epilepsy with centrotemporal spikes (BECTS).

METHODS Magnetoencephalography (MEG) was performed in 33 children with BECTS and 18 healthy children. Wechsler Intelligence Scale for Children, fourth edition (WISC-IV) was used to divide children with BECTS into two groups. Normal cognitive function was defined as a full-scale intelligence quotient (FSIQ) of >80, while decreased cognitive function was defined as a FSIQ of <80. Accumulated source imaging was used to evaluate the neuromagnetic source activity in multifrequency bands.

RESULTS Of the 33 patients with early untreated BECTS, a total of 17 had a FSIQ of <80 and 16 had FSIQ of >80. The course of epilepsy and number of seizures in the FSIQ <80 group were higher than that in the FSIQ >80 group. Our MEG results showed that in the 4-8 Hz frequency band, both patient groups had inactivation of the posterior cingulate cortex (PCC) region compared with the healthy control group. In the 30-80 Hz frequency band, the FSIQ <80 group showed inactivation of the PCC region compared with both the healthy control group and the FSIQ >80 group. In the 80-250 Hz frequency band, the FSIQ <80 group had inactivated of the medial frontal cortex (MFC) region compared with the healthy control group. In the 30-80 Hz frequency band, the strength of neuromagnetic source in patients with BECTS with FSIQ <80 was higher than that in the FSIQ >80 group and the healthy control group.

CONCLUSIONS The magnetic source inactivation of the MFC and PCC regions during the interictal time may be the reason for cognitive decline in early untreated children with BECTS. Children with BECTS with cognitive decline had a longer course of epilepsy and more seizures. The magnetic source localization in the 4-8 Hz frequency band may be a new imaging marker for the diagnosis of new BECTS.

Keywords: Accumulated source imaging, Benign childhood epilepsy with centrotemporal spikes, Cognitive function, Magnetoencephalography, Multifrequency bands

Epilepsy & behavior: E&B (2020), Vol. 112 (32858366) (6 citations)

Enhanced Fast-VESTAL for Magnetoencephalography Source Imaging: From Theory to Clinical Application in Epilepsy (2021)

Zheng, Li; Sheng, Jingwei; Cen, Zhehang; Teng, Pengfei; Wang, Jing; Wang, Qian; Lee, Roland Robert; Luan, Guoming; Huang, Mingxiong; Gao, Jia-Hong

ABSTRACT A novel magnetoencephalography source imaging approach called Fast Vector-based Spatio-Temporal Analysis (Fast-VESTAL) has been successfully applied in creating source images from evoked and resting-state data from both healthy subjects and individuals with neurological and/or psychiatric disorders, but its reconstructed source images may show false-positive activations, especially under low signal-to-noise ratio conditions. Here, to effectively reduce false-positive artifacts, we introduced an enhanced Fast-VESTAL (eFast-VESTAL) approach that adopts generalized second-order cone programming. We compared the spatiotemporal characteristics of the eFast-VESTAL approach to those of the popular distributed source approaches (e.g., the minimum L2-norm/mixed-norm methods) using computer simulations and auditory experiments. More importantly, we applied eFast-VESTAL to the presurgical evaluation of epilepsy. Our results demonstrated that eFast-VESTAL exhibited a lower dipole localization error and/or a higher correlation coefficient (CC) between the estimated source time series and ground truth under various conditions of source waveforms. Experimentally, eFast-VESTAL displayed more focal activation maps and a higher CC between the raw and predicted sensor data in response to auditory stimulation. Notably, eFast-VESTAL was the most accurate method for noninvasively detecting the epileptic zones determined using more invasive stereo-electroencephalography in the comparison.

IEEE transactions on bio-medical engineering (2021), Vol. 68, No. 3 (32790623) (1 citation)

Towards the Automatic Localization of the Irritative Zone Through Magnetic Source Imaging (2020)

Luria, Gianvittorio; Duran, Dunja; Visani, Elisa; Rossi Sebastiano, Davide; Sorrentino, Alberto; Tassi, Laura; Granvillano, Alice; Franceschetti, Silvana; Panzica, Ferruccio

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ABSTRACT The present work aims at validating a Bayesian multi-dipole modeling algorithm (SESAME) in the clinical scenario consisting of localizing the generators of single interictal epileptiform discharges from resting state magnetoencephalographic recordings. We use the results of Equivalent Current Dipole fitting, performed by an expert user, as a benchmark, and compare the results of SESAME with those of two widely used source localization methods, RAP-MUSIC and wMNE. In addition, we investigate the relation between post-surgical outcome and concordance of the surgical plan with the cerebral lobes singled out by the methods. Unlike dipole fitting, the tested algorithms do

not rely on any subjective channel selection and thus contribute towards making source localization more unbiased and automatic. We show that the two dipolar methods, SESAME and RAP-MUSIC, generally agree with dipole fitting in terms of identified cerebral lobes and that the results of the former are closer to the fitted equivalent current dipoles than those of the latter. In addition, for all the tested methods and particularly for SESAME, concordance with surgical plan is a good predictor of seizure freedom while discordance is not a good predictor of poor post-surgical outcome. The results suggest that the dipolar methods, especially SESAME, represent a reliable and more objective alternative to manual dipole fitting for clinical applications in the field of epilepsy surgery.

Keywords: Bayesian methods, Dipole modeling, Epilepsy, Magnetic source imaging, Magnetoencephalography

Brain topography (2020), Vol. 33, No. 5 (32770321) (4 citations)

Automatic and Accurate Epilepsy Ripple and Fast Ripple Detection via Virtual Sample Generation and Attention Neural Networks (2020)

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ABSTRACT About 1% of the population around the world suffers from epilepsy. The success of epilepsy surgery depends critically on pre-operative localization of epileptogenic zones. High frequency oscillations including ripples (80-250 Hz) and fast ripples (250-500 Hz) are commonly used as biomarkers to localize epileptogenic zones. Recent literature demonstrated that fast ripples indicate epileptogenic zones better than ripples. Thus, it is crucial to accurately detect fast ripples from ripples signals of magnetoencephalography for improving outcome of epilepsy surgery. This paper proposes an automatic and accurate ripple and fast ripple detection method that employs virtual sample generation and neural networks with an attention mechanism. We evaluate our proposed detector on patient data with 50 ripples and 50 fast ripples labeled by two experts. The experimental results show that our new detector outperforms multiple traditional machine learning models. In particular, our method can achieve a mean accuracy of 89.3% and an average area under the receiver operating characteristic curve of 0.88 in 50 repeats of random subsampling validation. In addition, we experimentally demonstrate the effectiveness of virtual sample generation, attention mechanism, and architecture of neural network models.

IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society (2020), Vol. 28, No. 8 (32746301) (5 citations)

Temporal-plus epilepsy in children: A connectomic analysis in magnetoencephalography (2020)

Martire, Daniel J; Wong, Simeon; Workewych, Adriana; Pang, Elizabeth; Boutros, Sarah; Smith, Mary Lou; Ochi, Ayako; Otsubo, Hiroshi; Sharma, Roy; Widjaja, Elysa; Snead, O Carter; Donner, Elizabeth; Ibrahim, George M

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OBJECTIVE Seizure recurrence following surgery for temporal lobe (TL) epilepsy may be related to extra-temporal epileptogenic foci, so-called temporal-plus (TL+) epilepsy. Here, we sought to leverage whole brain connectomic profiling in magnetoencephalography (MEG) to identify neural networks indicative of TL+ epilepsy in children.

METHODS Clinical and MEG data were analyzed for 121 children with TL and TL+ epilepsy spanning 20 years at the Hospital for Sick Children. Resting-state connectomes were derived using the weighted phase lag index from neuromagnetic oscillations. Multidimensional associations between patient connectomes, TL versus TL+ epilepsy, seizure freedom, and clinical covariates were performed using a partial least squares (PLS) analysis. Bootstrap resampling statistics were performed to assess statistical significance.

RESULTS A single significant latent variable representing 66% of the variance in the data was identified with significant contributions from extent of epilepsy (TL vs TL+), duration of illness, and underlying etiology. This component was associated with significant bitemporal and frontotemporal connectivity in the theta, alpha, and beta bands. By extracting a brain score, representative of the observed connectivity profile, patients with TL epilepsy were dissociated from those with TL+, independent of their postoperative seizure outcome.

SIGNIFICANCE By analyzing 121 connectomes derived from MEG data using a PLS approach, we find that connectomic profiling could dissociate TL from TL+ epilepsy. These findings may inform patient selection for resective procedures and guide decisions surrounding invasive monitoring.

Keywords: epilepsy, functional connectivity, neuroimaging, oscillations, phase-locking

Epilepsia (2020), Vol. 61, No. 8 (32619065) (10 citations)

Mapping language from MEG beta power modulations during auditory and visual naming (2020)

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ABSTRACT Evaluation of language dominance is an essential step prior to epilepsy surgery. There is no consensus on an optimal methodology for determining language dominance using magnetoencephalography (MEG). Oscillatory dynamics are increasingly recognized as being of fundamental importance for brain function and dysfunction. Using task-related beta power modulations in MEG, we developed an analysis framework for localizing and lateralizing areas relevant to language processing in patients with focal epilepsy. We examined MEG responses from 29 patients (age 42 ± 13 years, 15M/14F) during auditory description naming (ADN) and visual picture naming (PN). MEG data were preprocessed using a combination of spatiotemporal filtering, signal thresholding, and ICA decomposition. Beta-band 17-25Hz power decrements were examined at both sensor and source levels. Volumetric grids of anatomical source space were constructed in MNI space at 8 mm isotropic resolution, and beta-band power changes were estimated using the dynamic imaging of coherent sources beamformer technique. A 600 ms temporal-window that ends 100 ms before speech onset was selected for analysis, to focus on later stages of word production such as phonologic selection and motor speech preparation. Cluster-based permutation testing was employed for patient- and group-level statistical inferences. Automated anatomic labeling atlas-driven laterality indices (LIs) were computed for 13 left and right language- and motor speech-related cortical regions. Group localization of ADN and PN consistently revealed significant task-related decrements of beta-power within language-related areas in the frontal,

temporal and parietal lobes as well as motor-related regions of precentral/premotor and postcentral/somatomotor gyri. A region-of-interest analysis of ADN and PN suggested a strong correlation of $r = 0.74$ ($p < 0.05$, FDR corrected) between the two tasks within the language-related brain regions, with the highest spatial overlap in the prefrontal areas. Laterality indices (LIs) consistently showed left dominance (LI > 0.1) for most individuals (93% and 82% during ADN and PN, respectively), with average LIs of 0.40 ± 0.25 and 0.34 ± 0.20 for ADN and PN, respectively. Source analysis of task-related beta power decrements appears to be a reliable method for lateralizing and localizing brain activations associated with language processing in patients with epilepsy.

Keywords: Auditory description naming (ADN), DICS beamformer, Magnetoencephalography (MEG), Presurgical language mapping, Visual picture naming (PN)

NeuroImage (2020), Vol. 220 (32593799) (9 citations)

Relationship between epileptiform discharges and social reciprocity or cognitive function in children with and without autism spectrum disorders: An MEG study (2020)

Hirosawa, Tetsu; Sowman, Paul F; Fukai, Mina; Kameya, Masafumi; Soma, Daiki; Hino, Shoryoku; Kitamura, Tatsuru; An, Kyung-Min; Yoshimura, Yuko; Hasegawa, Chiaki; Saito, Daisuke; Ikeda, Takashi; Kikuchi, Mitsuru

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Psychiatry and clinical neurosciences (2020), Vol. 74, No. 9 (32588484) (1 citation)

Sensitivity of magnetoencephalography as a diagnostic tool for epilepsy: a prospective study (2020)

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ABSTRACT The diagnostic process for epilepsy can be lengthy and stressful, which may delay the start of treatment. The objective of this study was to determine the benefit of routine magnetoencephalography (MEG) with regard to diagnostic gain, compared to routine electroencephalography (EEG), EEG following sleep deprivation (EEGsd), and 24-hour EEG. In this prospective study, patients were included from two centres (Academic Centre for Epileptology Kempenhaeghe, Heeze and Elisabeth-Twee Steden Hospital, Tilburg) and MEG recording took place at a single centre (Amsterdam University Medical Centre, Vrije Universiteit Amsterdam) in The Netherlands. Consecutively referred patients from peripheral hospitals were included between August 2013 and March 2016. Patients were offered routine MEG in addition to EEG examination and MRI for the diagnosis of epilepsy. The final clinical diagnosis was based on all available clinical data and test results at the end of the diagnostic process. Sensitivity, specificity, and positive and negative predictive

values were calculated for routine EEG, routine EEG plus additional EEG and MEG. In addition, diagnostic gain associated with MEG, relative to the other modalities, was calculated. Secondary outcome was congruence of localization of epileptiform discharges between MEG and MRI or final clinical diagnosis. Based on a cohort of 138 patients, sensitivity and specificity was shown to be 31.6% and 78.4% for routine MEG, 31.6% and 100% for routine EEG, and 52.6% and 97.3% for routine EEG plus additional EEG, respectively. Routine MEG demonstrated a diagnostic gain of 16.8% compared to routine EEG and 9.5% compared to routine EEG plus additional EEG. In 35.7% of patients with a lesion on MRI that was consistent with the final clinical diagnosis, MEG showed epileptiform discharges in the same area. Routine MEG may provide additional value during the initial diagnosis of epilepsy.

Keywords: diagnosis, epilepsy, magnetoencephalography, sensitivity

Epileptic disorders: international epilepsy journal with videotape (2020), Vol. 22, No. 3 (32554358) (2 citations)

Spike-associated networks and intracranial electrographic findings (2020)

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ABSTRACT Functional connectivity is providing new insights into the network nature of epilepsy with growing clinical applications. Our objective was to validate a novel magnetoencephalography-based method to non-invasively measure the epileptic network. We retrospectively identified pediatric and adult patients with refractory focal epilepsy who underwent pre-surgical magnetoencephalography with subsequent intracranial electrographic monitoring. Magnetoencephalography tracings were visually reviewed, and interictal epileptiform discharges ("spikes") were individually marked. We then evaluated differences in whole-brain connectivity during brief epochs preceding the spikes and during the spikes using the Network-Based Statistic to test differences at the network level. In six patients with statistically-significant network differences, we observed substantial overlap between the spike-associated networks and electrographically active areas identified during intracranial monitoring (the spike-associated network was 78% and 83% sensitive for intracranial electroencephalography-defined regions in the irritative and seizure onset zones, respectively). These findings support the neurobiological validity of the spike-associated network method. Assessment of spike-associated networks has the potential to improve surgical planning in epilepsy surgery patients by identifying components of the epileptic network prior to implantation.

Keywords: epilepsy, functional connectivity, intracranial electroencephalography, magnetoencephalography

Epileptic disorders: international epilepsy journal with videotape (2020), Vol. 22, No. 3 (32554357) (2 citations)

Identifying the epileptogenic zone by four non-invasive imaging techniques versus stereo-EEG in MRI-negative pre-surgery epilepsy patients (2020)

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OBJECTIVE We evaluated four imaging techniques, i.e. Electroencephalography (EEG)-functional Magnetic Resonance Imaging (MRI) (EEG-fMRI), High-resolution EEG (HR-EEG), Magnetoencephalography (MEG) and 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (PET), for the identification of the epileptogenic zone (EZ) in 41 patients with negative MRI, candidate to neurosurgery.

METHODS For each technique, results were compared to the Stereo-EEG. Diagnostic measures were calculated with respect to the post-surgical outcome, either for all the patients (39/41, two patients excluded) and for the subgroup of patients with the EZ involving more than one lobe (20/41).

RESULTS When considered individually, each functional technique showed accuracy values ranging 54,6%-63,2%, having PET, MEG and HR-EEG higher sensitivity, and EEG-fMRI higher specificity. In patients with multilobar epileptogenic zone, functional techniques achieved the best accuracies (up to 80%) when three techniques, including EEG-fMRI, were considered together.

CONCLUSIONS The study highlights the accuracy of a combination of functional imaging techniques in the identification of EZ in MRI negative focal epilepsy. The best diagnostic yield was obtained if the combination of PET, MEG (or HR-EEG as alternative), EEG-fMRI were considered together.

SIGNIFICANCE The functional imaging techniques may improve the presurgical workup of MRI negative focal epilepsy, if epileptogenic zone involves more than one lobe.

Keywords: EEG-fMRI, Epilepsy surgery, HR-EEG, MEG, PET

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 8 (32544836) (19 citations)

Detection of interictal epileptiform discharges: A comparison of on-scalp MEG and conventional MEG measurements (2020)

Westin, Karin; Pfeiffer, Christoph; Andersen, Lau M; Ruffieux, Silvia; Cooray, Gerald; Kalaboukhov, Alexei; Winkler, Dag; Ingvar, Martin; Schneiderman, Justin; Lundqvist, Daniel

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OBJECTIVE Conventional MEG provides an unsurpassed ability to, non-invasively, detect epileptic activity. However, highly resolved information on small neuronal populations required in epilepsy diagnostics is lost and can be detected only intracranially. Next-generation on-scalp magnetencephalography (MEG) sensors aim to retrieve information unavailable to conventional non-invasive brain imaging techniques. To evaluate the benefits of on-scalp MEG in epilepsy, we performed the first-ever such measurement on an epilepsy patient.

METHODS Conducted as a benchmarking study focusing on interictal epileptiform discharge (IED) detectability, an on-scalp high-temperature superconducting quantum interference device magnetometer (high-Tc SQUID) system was compared to a conventional, low-temperature SQUID system. Co-registration of

electroencephalopraphy (EEG) was performed. A novel machine learning-based IED-detection algorithm was developed to aid identification of on-scalp MEG unique IEDs.

RESULTS Conventional MEG contained 24 IEDs. On-scalp MEG revealed 47 IEDs (16 co-registered by EEG, 31 unique to the on-scalp MEG recording).

CONCLUSION Our results indicate that on-scalp MEG might capture IEDs not seen by other non-invasive modalities.

SIGNIFICANCE On-scalp MEG has the potential of improving non-invasive epilepsy evaluation.

Keywords: Epilepsy, High-critical temperature SQUIDs, Instrumentation, Interictal epileptiform discharges, Magnetoencephalography

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 8 (32504930) (3 citations)

Insular Magnetoencephalography Dipole Clusters in Patients With Refractory Focal Epilepsy (2021)

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PURPOSE The clinical significance of magnetoencephalography (MEG) dipole clusters in the insular region in patients with focal epilepsy, when present in conjunction with MEG dipole clusters in other regions of the brain is not known.

METHODS All patients (adult and pediatric) with MEG dipole clusters involving the insula were retrospectively evaluated. Patients who underwent any form of surgical intervention were included in the study. Data obtained included age, sex, seizure characteristics, MRI brain, EEG, MEG, intracranial EEG, type of intervention, and seizure outcomes.

RESULTS Twenty-four patients (12 adults and 12 pediatric) were included. Eight patients had one staged intervention and 16 had intracranial evaluation. Ten of 11 patients (91%) with insular coverage by stereotactic EEG had interictal insular spikes, and 5 of 11 patients (45%) had ictal onset from the insula. Combined Engel (I & II) outcomes were seen in five patients with resections/ablations involving the insula MEG dipole clusters as compared with eight patients where the insular MEG dipole clusters were not resected/ablated.

CONCLUSIONS Insular MEG dipole clusters identified on surface MEG correlated with interictal spikes in intracranial stereotactic electrode contacts in the insula. The presence of insular MEG dipole clusters, however, does not definitively imply a primary insular onset epilepsy.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2021), Vol. 38, No. 6 (32501951) (4 citations)

Evidence From Meta-Analysis Supports Ictal Magnetoencephalographic Source Imaging as an Accurate Method in Presurgery Evaluation of Patients With Drug-Resistant Epilepsy (2020)

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BACKGROUND. Successful epilepsy surgery relies on localization and removal of the brain area responsible for initializing the seizures called the epileptogenic zone (EZ). Intracranial EEG (icEEG) is gold standard of this localization but has several limitations like invasiveness and limited covered area. A noninvasive method with accurate localization precision is therefore desir-

able. The aim of this article is to investigate the following hypotheses: (1) Ictal onset zone as localized by magnetic source imaging (iMSI) can reliably localize the EZ in focal epilepsy and (2) this localization is as good as that of icEEG.

METHODS. Six original studies and a total of 59 unique patients were included in a meta-analysis.

RESULTS. Sensitivity and specificity of iMSI based on surgery outcome were 77% (95% CI 60%-90%) and 75% (95% CI 53%-90%), respectively. Specificity of iMSI was statistically higher than that of icEEG. There was no significant difference between sensitivity of iMSI and icEEG.

CONCLUSION. The meta-analysis supports that iMSI is an accurate method, achieving similar sensitivity and higher specificity than icEEG. However, at present the use of the method is limited by short recording times. A limitation that might be overcome in the future using technical advances.

Keywords: epilepsy, epilepsy surgery, ictal, magnetoencephalography, meta-analysis, source localization

Clinical EEG and neuroscience (2020), Vol. 51, No. 6 (32437218) (1 citation)

Intravenous dexmedetomidine sedation for magnetoencephalography: A retrospective study (2020)

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BACKGROUND Magnetoencephalography (MEG) plays a preponderant role in the preoperative assessment of patients with drug-resistant epilepsy (DRE). However, the magnetoencephalography of patients with drug-resistant epilepsy can be difficult without sedation and/or general anesthesia. Our objective is to describe our experience with intravenous dexmedetomidine as sedation for magnetoencephalography and its effect, if any, on the ability to recognize epileptic spikes.

METHODS In this retrospective study, we reviewed the records of 89 children who presented for Magnetoencephalography/electroencephalography (EEG) scans between August of 2008 and May of 2015. Data analyzed included demographics and the frequency of epileptic spikes. Sedated magnetoencephalography recordings were compared to nonsedated video-electroencephalography (vEEG) recordings in the same patients to determine the impact of dexmedetomidine.

RESULTS Spike frequency between magnetoencephalography with sedation and video-electroencephalography without sedation was compared in 85 patients. Magnetoencephalography and video-electroencephalography were considered clinically concordant in 80 patients (94.1%) and discordant in 5 patients (5.9%), all with less spikes during Magnetoencephalography. The median (range) bolus dose of dexmedetomidine was 2 (1-2) mcg/kg. The median (range) infusion rate of dexmedetomidine was 2 (0.5-4) mcg/kg/h. All patients experienced reductions in heart rate after administration of dexmedetomidine; these reductions were statistically, but not clinically, significant.

CONCLUSIONS Our results suggest that dexmedetomidine-based protocol provides reliable sedation in children undergoing MEG scanning because of the high success rate, limited interictal artifacts, and minimal impacts on spike frequency.

Keywords: dexmedetomidine, electroencephalography (EEG), intractable epilepsy, magnetoencephalography (MEG), sedation, spike identification

Paediatric anaesthesia (2020), Vol. 30, No. 7 (32436319) (3 citations)

Preoperative localization of seizure onset zones by magnetic source imaging, EEG-correlated functional MRI, and their combination (2020)

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OBJECTIVE Preoperative localization of seizure onset zones (SOZs) is an evolving field in the treatment of refractory epilepsy. Both magnetic source imaging (MSI), and the more recent EEG-correlated functional MRI (EEG-fMRI), have shown applicability in assisting surgical planning. The purpose of this study was to evaluate the capability of each method and their combination in localizing the seizure onset lobe (SL).

METHODS The study included 14 patients who underwent both MSI and EEG-fMRI before undergoing implantation of intracranial EEG (icEEG) as part of the presurgical planning of the resection of an epileptogenic zone (EZ) during the years 2012-2018. The estimated location of the SL by each method was compared with the location determined by icEEG. Identification rates of the SL were compared between the different methods.

RESULTS MSI and EEG-fMRI showed similar identification rates of SL locations in relation to icEEG results (88% ± 31% and 73% ± 42%, respectively; $p = 0.281$). The additive use of the coverage lobes of both methods correctly identified 100% of the SL, significantly higher than EEG-fMRI alone ($p = 0.039$) and nonsignificantly higher than MSI ($p = 0.180$). False-identification rates of the additive coverage lobes were significantly higher than MSI ($p = 0.026$) and EEG-fMRI ($p = 0.027$). The intersecting lobes of both methods showed the lowest false identification rate (13% ± 6%, $p = 0.01$).

CONCLUSIONS Both MSI and EEG-fMRI can assist in the presurgical evaluation of patients with refractory epilepsy. The additive use of both tests confers a high identification rate in finding the SL. This combination can help in focusing implantation of icEEG electrodes targeting the SOZ.

Keywords: EEG-fMRI, MSI, icEEG, magnetic source imaging, refractory epilepsy, seizure onset zone

Journal of neurosurgery (2020), Vol. 134, No. 3 (32413858) (2 citations)

Lateralization of epilepsy using intra-hemispheric brain networks based on resting-state MEG data (2020)

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ABSTRACT Focal epilepsy originates within networks in one hemisphere. However, previous studies have investigated network topologies for the entire brain. In this study, magnetoencephalography (MEG) was used to investigate functional intra-hemispheric networks of healthy controls (HCs) and patients with left- or right-hemispheric temporal lobe or temporal plus extra-temporal lobe epilepsy. 22 HCs, 25 left patients (LPs), and 16 right patients (RPs) were enrolled. The debiased weighted phase lag index was used to calculate functional connectivity between 246 brain regions in six frequency bands. Global efficiency, characteristic path length, and transitivity were computed for left and right intra-hemispheric networks. The right global graph measures (GGMs) in the theta band were significantly different ($p < .005$) between RPs and both LPs and HCs. Right and left GGMs in higher frequency bands were significantly different ($p < .05$) between HCs and the patients. Right GGMs were used as input features of a Naïve-Bayes classifier to classify LPs and RPs (78.0% accuracy) and all three groups (75.5% accuracy). The complete theta band brain networks were compared between LPs and RPs with network-based statistics (NBS) and with the clustering coefficient (CC), nodal efficiency (NE), betweenness centrality (BC), and eigenvector centrality (EVC). NBS identified a subnetwork primarily composed of right intra-hemispheric connections. Significantly different ($p < .05$) nodes were primarily in the right hemisphere for the CC and NE and primarily in the left hemisphere for the BC and EVC. These results indicate that intra-hemispheric MEG networks may be incorporated in the diagnosis and lateralization of focal epilepsy.

Keywords: focal epilepsy, functional connectivity, graph measures, intra-hemispheric brain networks, machine learning, magnetoencephalography, network-based statistics

Human brain mapping (2020), Vol. 41, No. 11 (32400923) (10 citations)

Accuracy and spatial properties of distributed magnetic source imaging techniques in the investigation of focal epilepsy patients (2020)

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ABSTRACT Source localization of interictal epileptiform discharges (IEDs) is clinically useful in the presurgical workup of epilepsy patients. We aimed to compare the performance of four different distributed magnetic source imaging (dMSI) approaches: Minimum norm estimate (MNE), dynamic statistical parametric mapping (dSPM), standardized low-resolution electromagnetic tomography (sLORETA), and coherent maximum entropy on the mean (cMEM). We also evaluated whether a simple average of maps obtained from multiple inverse solutions (Ave) can improve localization accuracy. We analyzed dMSI of 206 IEDs derived from magnetoencephalography recordings in 28 focal epilepsy patients who had a well-defined focus determined through intracranial EEG (iEEG), epileptogenic MRI lesions or surgical resection. dMSI accuracy and spatial properties were quantitatively estimated as: (a) distance from the epilepsy focus, (b) reproducibility, (c) spatial dispersion (SD), (d) map extension, and (e) effect of thresholding on map properties. Clinical performance was excellent for all methods (median distance from the focus MNE = 2.4 mm; sLORETA = 3.5 mm; cMEM = 3.5 mm; dSPM = 6.8 mm, Ave = 0 mm). Ave showed the lowest distance between the map maximum and epilepsy focus (Dmin lower than cMEM, MNE, and dSPM, $p = .021$, $p = .008$, $p < .001$, respectively). cMEM showed the best spatial features, with lowest SD outside the focus (SD lower than all other methods, $p < .001$ consistently) and high contrast between the generator and surrounding regions. The average map Ave provided the best localization accuracy, whereas cMEM exhibited the lowest amount of spurious distant activity. dMSI techniques have the potential to significantly improve identification of iEEG targets and to guide surgical planning, especially when multiple methods are combined.

Keywords: MEG, interictal epileptiform discharges, inverse problem, magnetic source imaging, presurgical evaluation, source localization, spike

Human brain mapping (2020), Vol. 41, No. 11 (32386115) (16 citations)

Genuine cross-frequency coupling networks in human resting-state electrophysiological recordings (2020)

Siebenhühner, Felix; Wang, Sheng H; Arnulfo, Gabriele; Lampinen, Anna; Nobili, Lino; Palva, J Matias; Palva, Satu

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ABSTRACT Phase synchronization of neuronal oscillations in specific frequency bands coordinates anatomically distributed neuronal processing and communication. Typically, oscillations and synchronization take place concurrently in many distinct frequencies, which serve separate computational roles in cognitive functions. While within-frequency phase synchronization has been studied extensively, less is known about the mechanisms that govern neuronal processing distributed across frequencies and brain regions. Such integration of processing between frequencies could be achieved via cross-frequency coupling (CFC), either by phase-amplitude coupling (PAC) or by n:m-cross-frequency phase synchrony (CFS). So far, studies have mostly focused on local CFC in individual brain regions, whereas the presence and functional organization of CFC between brain areas have remained largely unknown. We posit that interareal CFC may be essential for large-scale coordination of neuronal activity and investigate here whether genuine CFC networks are present in human resting-state (RS) brain activity. To assess the functional organization of CFC networks, we identified brain-wide CFC networks at mesoscale resolution from stereoelectroencephalography (SEEG) and at macroscale resolution from source-reconstructed magnetoencephalography (MEG) data. We developed a novel, to our knowledge, graph-theoretical method to distinguish genuine CFC from spurious CFC that may arise from nonsinusoidal signals ubiquitous in neuronal activity. We show that genuine interareal CFC is present in human RS activity in both SEEG and MEG data. Both CFS and PAC networks coupled theta and alpha oscillations with higher frequencies in large-scale networks connecting anterior and posterior brain regions. CFS and PAC networks had distinct spectral patterns and opposing distribution of low- and high-frequency network hubs, implying that they constitute distinct CFC mechanisms. The strength of CFS networks was also predictive of cognitive performance in a separate neuropsychological assessment. In conclusion, these results provide evidence for interareal CFS and PAC being 2 distinct mechanisms for coupling oscillations across frequencies in large-scale brain networks.

PLoS biology (2020), Vol. 18, No. 5 (32374723) (25 citations)

A Combination of Particle Swarm Optimization and Minkowski Weighted K-Means Clustering: Application in Lateralization of Temporal Lobe Epilepsy (2020)

Jamali-Dinan, Samira-Sadat; Soltanian-Zadeh, Hamid; Bowyer, Susan M; Almohri, Haidar; Dehghani, Hamed; Elisevich, Kost; Nazem-Zadeh, Mohammad-Reza

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ABSTRACT K-Means is one of the most popular clustering algorithms that partitions observations into nonoverlapping subgroups based on a predefined similarity metric. Its drawbacks include a sensitivity to noisy features and a dependency of its resulting clusters upon the initial selection of cluster centroids resulting in the algorithm converging to local optima. Minkowski weighted K-Means (MWK-Means) addresses the issue of sensitivity to noisy features, but is sensitive to the initialization of clusters, and so the algorithm may similarly converge to local optima. Particle Swarm Optimization (PSO) uses a globalized search method to solve this issue. We present a hybrid Particle Swarm Optimization (PSO) + MWK-Means clustering algorithm to address all the above problems in a single framework, while maintaining benefits of PSO and MWK Means methods. This study investigated the utility of this approach in lateralizing the epileptogenic hemisphere for temporal lobe epilepsy (TLE) cases using magnetoencephalography (MEG) coherence source imaging (CSI) and diffusion tensor imaging (DTI). Using MEG-CSI, we analyzed preoperative resting state MEG data from 17 adults TLE patients with Engel class I outcomes to determine coherence at 54 anatomical sites and compared the results with 17 age- and gender-matched controls. Fiber-tracking was performed through the same anatomical sites using DTI data. Indices of both MEG coherence and DTI nodal degree were calculated. A PSO + MWK-Means clustering algorithm was applied to identify the side of temporal lobe epileptogenicity and distinguish between normal and TLE cases. The PSO module was aimed at identifying initial cluster centroids and assigning initial feature weights to cluster centroids and, hence, transferring to the MWK-Means module for the final optimal clustering solution. We demonstrated improvements with the use of the PSO + MWK-Means clustering algorithm compared to that of K-Means and MWK-Means independently. PSO + MWK-Means was able to successfully distinguish between normal and TLE in 97.2% and 82.3% of cases for DTI and MEG data, respectively. It also lateralized left and right TLE in 82.3% and 93.6% of cases for DTI and MEG data, respectively. The proposed optimization and clustering methodology for MEG and DTI features, as they relate to focal epileptogenicity, would enhance the identification of the TLE laterality in cases of unilateral epileptogenicity.

Keywords: Coherence, Diffusion tensor imaging, Functional connectivity, Magnetoencephalography, Minkowski weighted K-means clustering, Nodal degree, Particle swarm optimization, Structural connectivity, Temporal lobe epilepsy

Brain topography (2020), Vol. 33, No. 4 (32347472) (2 citations)

Merging Magnetoencephalography into Epilepsy Presurgical Work-up Under the Framework of Multimodal Integration (2020)

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ABSTRACT Multimodal image integration is the procedure that puts together imaging data from multiple sources into the same space by a computerized registration process. This procedure is relevant to patients with difficult-to-localize epilepsy undergoing presurgical evaluation, who typically have many tests performed, including MR imaging, PET, ictal single-photon emission computed tomography, magnetoencephalography (MEG), and intracranial electroencephalogram (EEG). This article describes the methodology of such integration, focusing on integration of MEG. Also discussed is the clinical value of integration of MEG, in terms of planning of intracranial EEG implantation, interpretation of intracranial EEG data, planning of final resection, and addressing surgical failures.

Keywords: Epilepsy, ICEEG, MEG, Multimodal, Presurgical evaluation, SEEG

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336411) (2 citations)

MEG for Greater Sensitivity and More Precise Localization in Epilepsy (2020)

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ABSTRACT Magnetoencephalography is the non-invasive measurement of miniscule magnetic fields

produced by brain electrical currents, and is used most fruitfully to evaluate epilepsy patients. While other modalities infer brain function indirectly by measuring changes in blood flow, metabolism, and oxygenation, magnetoencephalography measures neuronal and synaptic function directly with submillisecond temporal resolution. The brain's magnetic field is recorded by neuromagnetometers surrounding the head in a helmet-shaped sensor array. Because magnetic signals are not distorted by anatomy, magnetoencephalography allows for a more accurate measurement and localization of brain activities than electroencephalography. Magnetoencephalography has become an indispensable part of the armamentarium at epilepsy centers.

Keywords: Dipole, Gradiometer, Head model, Magnetic source imaging, Magnetoencephalography, Magnetometer, Source localization, Source model

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336403) (5 citations)

Juvenile myoclonic epilepsy shows increased posterior theta, and reduced sensorimotor beta resting connectivity (2020)

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BACKGROUND Widespread structural and functional brain network changes have been shown in Juvenile Myoclonic Epilepsy (JME) despite normal clinical neuroimaging. We sought to better define these changes using magnetoencephalography (MEG) and source space connectivity analysis for optimal neurophysiological and anatomical localisation.

METHODS We consecutively recruited 26 patients with JME who underwent resting state MEG recording, along with 26 age-and-sex matched controls. Whole brain connectivity was determined through correlation of Automated Anatomical Labelling (AAL) atlas source space MEG timeseries in conventional frequency bands of interest delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (40-60 Hz). We used a Linearly Constrained Minimum Variance (LCMV) beamformer to extract voxel wise time series of 'virtual sensors' for the desired frequency bands, followed by connectivity analysis using correlation between frequency- and node-specific power fluctuations, for the voxel maxima in each AAL atlas label, correcting for noise, potentially spurious connections and multiple comparisons.

RESULTS We found increased connectivity in the theta band in posterior brain regions, surviving statistical correction for multiple comparisons (corrected $p < 0.05$), and decreased connectivity in the beta band in sensorimotor cortex, between right pre- and post- central gyrus ($p < 0.05$) in JME compared to controls.

CONCLUSIONS Altered resting-state MEG connectivity in JME comprised increased connectivity in posterior theta - the frequency band associated with long range connections affecting attention and arousal - and decreased beta-band sensorimotor connectivity. These findings likely relate to altered regulation of the sensorimotor network and seizure prone states in JME.

Keywords: Connectivity, JME, Juvenile myoclonic epilepsy, MEG, Magnetoencephalography

Epilepsy research (2020), Vol. 163 (32335503) (14 citations)

The value of magnetoencephalography for stereo-EEG-guided radiofrequency thermocoagulation in MRI-negative epilepsy (2020)

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OBJECTIVE Magnetoencephalography (MEG) is valuable for guiding resective surgery in patients with epilepsy. However, its value for minimally invasive treatment is still unknown. This study aims to evaluate the value of MEG for stereo-electroencephalogram (EEG)-guided radiofrequency thermocoagulation (SEEG-guided RF-TC) in magnetic resonance imaging (MRI)-negative epilepsies.

METHODS An observational cohort study was performed and 19 MRI-negative patients who underwent SEEG-guided RF-TC in our epilepsy center were included. In addition, 16 MRI-positive patients were included as a reference group. Semiology, electrophysiology, and imaging information were collected. To evaluate the value of locating the MEG cluster, the proportion of the RF-TC contacts located in the MEG cluster out of all contacts used to perform RF-TC in each patient was calculated. All patients underwent the standard SEEG-guided RF-TC procedure and were followed up after the treatment.

RESULTS Nineteen MRI-negative patients were divided into two groups based on the existence of MEG clusters; 10 patients with MEG clusters were in group I and nine patients without any MEG cluster were in group II. No significant difference was observed in terms of age, sex, type of seizures, or number of SEEG electrodes implanted. The median of the proportion of contacts in the MEG cluster was 77.0 % (IQR 57.7-100.0 %). The follow-up results showed that the probability of being seizure-free at one year after RFTC in MRI-negative patients with an MEG cluster was 30.0 % (95 % CI 11.6-77.3 %), significantly (p = 0.014) higher than that in patients without an MEG cluster; there was no significant difference when compared with MRI-positive patients.

CONCLUSION This is the first study to evaluate the value of MEG in SEEG-guided RF-TC in MRI-negative epilepsies. MEG is a useful supplement for patients with MRI-negative epilepsy. MEG can be applied in minimally invasive treatment. MEG clusters can help identify better candidates and provide a valuable target for SEEG-guided RF-TC, which leads to better outcomes.

Epilepsy research (2020), Vol. 163 (32278277) (4 citations)

Relative contribution of individual versus combined functional imaging studies in predicting seizure freedom in pediatric epilepsy surgery: an area under the curve analysis (2020)

Kankirawatana, Pongkiat; Mohamed, Ismail S; Lauer, Jason; Aban, Inmaculada; Kim, Hyunmi; Li, Rong; Harrison, Allan; AS; Goyal, Monisha; Rozzelle, Curtis J; Knowlton, Robert; Blount, Jeffrey P

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OBJECTIVE The goal of this study was to evaluate the predictive value and relative contribution of noninvasive presurgical functional imaging modalities based on the authors' institutional experience in pursuing seizure-free surgical outcomes in children with medically refractory epilepsy.

METHODS This was a retrospective, single-institution, observational cohort study of pediatric patients who underwent evaluation and surgical treatment for medically refractory partial epilepsy between December 2003 and June 2016. During this interval, 108 children with medically refractory partial epilepsy underwent evaluation for localization and resective epilepsy surgery. Different noninvasive functional imaging modalities, including ictal SPECT, FDG-PET, and magnetoencephalography-magnetic source imaging, were utilized to augment a standardized paradigm (electroencephalography/semiology, MRI, and neuropsychology findings) for localization. Outcomes were evaluated at a minimum of 2 years (mean 7.5 years) utilizing area under the receiver operating characteristic curve analysis. Localizing modalities and other clinical covariates were examined in relation to long-term surgical outcomes.

RESULTS There was variation in the contribution of each test, and no single presurgical workup modality could singularly and reliably predict a seizure-free outcome. However, concordance of presurgical modalities yielded a high predictive value. No difference in long-term outcomes between inconclusive (normal or diffusely abnormal) and abnormal focal MRI results were found. Long-term survival analyses revealed a statistically significant association between seizure freedom and patients with focal ictal EEG, early surgical intervention, and no history of generalized convulsions.

CONCLUSIONS Comprehensive preoperative evaluation utilizing multiple noninvasive functional imaging modalities is not redundant and can improve pediatric epilepsy surgical outcomes.

Keywords: AUC = area under the ROC curve, EEG = electroencephalography, MEG-MSI = magnetoencephalography–magnetic source imaging, PMC = patient management conference, ROC = receiver operating characteristic, epilepsy surgery, outcome, pediatric epilepsy, presurgical workup

Neurosurgical focus (2020), Vol. 48, No. 4 (32234993) (2 citations)

Utility of magnetic source imaging in nonlesional focal epilepsy: a prospective study (2020)

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OBJECTIVE For patients with nonlesional refractory focal epilepsy (NLRFE), localization of the epileptogenic zone may be more arduous than for other types of epilepsy and frequently requires information from multiple noninvasive presurgical modalities and intracranial EEG (icEEG). In this prospective, blinded study, the authors assessed the clinical added value of magnetic source imaging (MSI) in the presurgical evaluation of patients with NLRFE.

METHODS This study prospectively included 57 consecutive patients with NLRFE who were considered for epilepsy surgery. All patients underwent noninvasive presurgical evaluation and then MSI. To determine the surgical plan, discussion of the results of the presurgical evaluation was first undertaken while discussion participants were blinded to the MSI results. MSI results were then presented. MSI influence on the initial management plan was assessed.

RESULTS MSI results influenced patient management in 32 patients. MSI results led to the following changes in surgical strategy in 14 patients (25%): allowing direct surgery in 6 patients through facilitating the detection of subtle cortical dysplasia in 4 patients and providing

additional concordant diagnostic information to other presurgical workup in another 2 patients; rejection of surgery in 3 patients originally deemed surgical candidates; change of plan from direct surgery to icEEG in 2 patients; and allowing icEEG in 3 patients deemed not surgical candidates. MSI results led to changed electrode locations and contact numbers in another 18 patients. Epilepsy surgery was performed in 26 patients influenced by MSI results and good surgical outcome was achieved in 21 patients.

CONCLUSIONS This prospective, blinded study showed that information provided by MSI allows more informed icEEG planning and surgical outcome in a significant percentage of patients with NLRFE and should be included in the presurgical workup in those patients.

Keywords: ATL = anterior temporal lobectomy, ECD = equivalent current dipole, EMSI = electromagnetic source imaging, EZ = epileptogenic zone, MEG = magnetoencephalography, MSI = magnetic source imaging, NLRFE = nonlesional refractory focal epilepsy, SEEG = stereo-electroencephalography, VEEG = video-EEG, epilepsy surgery, icEEG = intracranial EEG, magnetoencephalography, nonlesional, prospective study

Neurosurgical focus (2020), Vol. 48, No. 4 (32234989) (9 citations)

Distributed source analysis of magnetoencephalography using a volume head model combined with statistical methods improves focus diagnosis in epilepsy surgery (2020)

Ishizaki, Tomotaka; Maesawa, Satoshi; Nakatsubo, Daisuke; Yamamoto, Hiroyuki; Takai, Sou; Shibata, Masashi; Kato, Sachiko; Natsume, Jun; Hoshiyama, Minoru; Wakabayashi, Toshihiko

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ABSTRACT Deep-seated epileptic focus estimation using magnetoencephalography is challenging because of its low signal-to-noise ratio and the ambiguity of current sources estimated by interictal epileptiform discharge (IED). We developed a distributed source (DS) analysis method using a volume head model as the source space of the forward model and standardized low-resolution brain electromagnetic tomography combined with statistical methods (permutation tests between IEDs and baselines and false discovery rate between voxels to reduce variation). We aimed to evaluate the efficacy of the combined DS (cDS) analysis in surgical cases. In total, 19 surgical cases with adult and pediatric focal epilepsy were evaluated. Both cDS and equivalent current dipole (ECD) analyses were performed in all cases. The concordance rates of the two methods with surgically identified epileptic foci were calculated and compared with surgical outcomes. Concordance rates from the cDS analysis were significantly higher than those from the ECD analysis (68.4% vs. 26.3%), especially in cases with deep-seated lesions, such as in the interhemispheric, fronto-temporal base, and mesial temporal structures (81.8% vs. 9.1%). Furthermore, the concordance rate correlated well with surgical outcomes. In conclusion, cDS analysis has better diagnostic performance in focal epilepsy, especially with deep-seated epileptic focus, and potentially leads to good surgical outcomes.

Scientific reports (2020), Vol. 10, No. 1 (32210314) (0 citations)

Interictal structural and functional connectivity in idiopathic generalized epilepsy: A systematic review of graph theoretical studies (2020)

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ABSTRACT The evaluation of the role of anomalous neuronal networks in epilepsy using a graph theoretical approach is of growing research interest. There is currently no consensus on optimal methods for performing network analysis, and it is possible that variations in study methodology account for diverging findings. This review focuses on global functional and structural interictal network characteristics in people with idiopathic generalized epilepsy (IGE) with the aim of appraising the methodological approaches used and assessing for meaningful consensus. Thirteen studies were included in the review. Data were heterogenous and not suitable for meta-analysis. Overall, there is a suggestion that the cerebral neuronal networks of people with IGE have different global structural and functional characteristics to people without epilepsy. However, the nature of the aberrations is inconsistent with some studies demonstrating a more regular network configuration in IGE, and some, a more random topology. There is greater consistency when different data modalities and connectivity subtypes are compared separately, with a tendency towards increased small-worldness of networks in functional electroencephalography/magnetoencephalography (EEG/MEG) studies and decreased small-worldness of networks in structural studies. Prominent variation in study design at all stages is likely to have contributed to differences in study outcomes. Despite increasing literature surrounding neuronal network analysis, systematic methodological studies are lacking. Absence of consensus in this area significantly limits comparison of results from different studies, and the ability to draw firm conclusions about network characteristics in IGE.

Keywords: Connectome, EEG, Graph theory, IGE, Network analysis, fMRI

Epilepsy & behavior: E&B (2020), Vol. 106 (32193094) (20 citations)

Magnetoencephalography resting state connectivity patterns as indicatives of surgical outcome in epilepsy patients (2020)

Aydin, Ümit; Pellegrino, Giovanni; Ali, Obaï Bin Ka'b; Abdallah, Chifaou; Dubeau, François; Lina, Jean-Marc; Kobayashi, Eliane; Grova, Christophe

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OBJECTIVE Focal epilepsy is a disorder affecting several brain networks; however, epilepsy surgery usually targets a restricted region, the so-called epileptic focus. There is a growing interest in embedding resting state (RS) connectivity analysis into pre-surgical workup.

APPROACH In this retrospective study, we analyzed Magnetoencephalography (MEG) long-range RS functional connectivity patterns in patients with drug-resistant focal epilepsy. MEG recorded prior to surgery from seven seizure-free (Engel Ia) and five non seizure-free (Engel III or IV) patients were analyzed (minimum 2-years post-surgical follow-up). MEG segments without any detectable epileptic activity were source localized using wavelet-based Maximum Entropy on the Mean method. Amplitude envelope correlation in the theta (4-8 Hz), alpha (8-13 Hz), and beta (13-26 Hz) bands were used for assessing connectivity.

MAIN RESULTS For seizure-free patients, we found an isolated epileptic network characterized by weaker connections between the brain region where interictal epileptic discharges (IED) are generated and the rest of the cortex, when compared to connectivity between the corresponding contralateral homologous region and the rest of the cortex. Contrarily, non seizure-free

patients exhibited a widespread RS epileptic network characterized by stronger connectivity between the IED generator and the rest of the cortex, in comparison to the contralateral region and the cortex. Differences between the two seizure outcome groups concerned mainly distant long-range connections and were found in the alpha-band.

SIGNIFICANCE Importantly, these connectivity patterns suggest specific mechanisms describing the underlying organization of the epileptic network and were detectable at the individual patient level, supporting the prospect use of MEG connectivity patterns in epilepsy to predict post-surgical seizure outcome.

Journal of neural engineering (2020), Vol. 17, No. 3 (32191632) (17 citations)

The Clinical Utility of Transcranial Magnetic Stimulation in Determining Hemispheric Dominance for Language: A Magnetoencephalography Comparison Study (2020)

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PURPOSE Transcranial magnetic stimulation (TMS) has recently emerged as a noninvasive alternative to the intracarotid sodium amytal (Wada) procedure for establishing hemispheric dominance (HD) for language. The accuracy of HD determined by TMS was examined by comparing against the HD derived by magnetoencephalography (MEG), a prominent clinical technique with excellent concordance with the Wada procedure.

METHODS Sixty-seven patients (54 patients ≤18 years) underwent language mapping with TMS and MEG as part of clinical epilepsy and tumor presurgical assessment. Language was mapped in MEG during an auditory word recognition paradigm, and a laterality index was calculated using the number of dipoles and their spatial extent in the two hemispheres. Transcranial magnetic stimulation language mapping was performed as patients performed a naming task, and TMS-induced speech disruptions were recorded during 5-Hz TMS applied to anterior and posterior language cortices. Transcranial magnetic stimulation laterality index was estimated using the number and type of speech disruption in the language regions of each hemisphere.

RESULTS Transcranial magnetic stimulation and MEG estimates of HD were concordant in 42 (63%) patients, resulting in a sensitivity of 74% and a specificity of 72%. The overall accuracy of TMS was 73%, equivalent to an odds ratio of 7.35.

CONCLUSIONS In this first large-scale comparative study in a clinical population, we demonstrate that TMS is a safe and reliable noninvasive tool in determining HD for language. Improving the accuracy of TMS by optimizing TMS parameters and improving task choice will further facilitate the use of TMS to characterize language function, especially in pediatrics.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2020), Vol. 37, No. 2 (32142020) (6 citations)

Optically pumped magnetoencephalography in epilepsy (2020)

Vivekananda, Umesh; Mellor, Stephanie; Tierney, Tim M; Holmes, Niall; Boto, Elena; Leggett, James; Roberts, Gillian; Hill, Ryan M; Litvak, Vladimir; Brookes, Matthew J; Bowtell, Richard; Barnes, Gareth R; Walker, Matthew C

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ABSTRACT We demonstrate the first use of Optically Pumped Magnetoencephalography (OP-MEG) in an epilepsy patient with unrestricted head movement. Current clinical MEG uses a traditional SQUID system, where sensors are cryogenically cooled and housed in a helmet in which the patient's head is fixed. Here, we use a different type of sensor (OPM), which operates at room temperature and can be placed directly on the patient's scalp, permitting free head movement. We performed OP-MEG recording in a patient with refractory focal epilepsy. OP-MEG-identified analogous interictal activity to scalp EEG, and source localized this activity to an appropriate brain region.

Annals of clinical and translational neurology (2020), Vol. 7, No. 3 (32112610) (14 citations)

Frequency-specific changes in the default mode network in patients with cingulate gyrus epilepsy (2020)

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ABSTRACT To identify abnormal functional connectivity of the default mode network in cingulate gyrus epilepsy, which may yield new information about the default mode network and suggest a new cingulate gyrus epilepsy biomarker. Fifteen patients with cingulate gyrus epilepsy (mean age = 21 years) and 15 healthy controls (mean age = 24 years) were studied in the resting state using magnetoencephalography. Twelve brain areas of interest in the default mode network were extracted and investigated with multifrequency signals that included alpha (α, 8-13 Hz), beta (β, 14-30 Hz), and gamma (γ, 31-80 Hz) band oscillations. Patients with cingulate gyrus epilepsy had significantly greater connectivity in all three frequency bands (α, β, γ). A frequency-specific elevation of functional connectivity was found in patients compared to controls. The greater functional connectivity in the γ band was significantly more prominent than that of the α and β bands. Patients with cingulate gyrus epilepsy and controls differed significantly in functional connectivity between the left angular gyrus and left posterior cingulate cortex in the α, β, and γ bands. The results of the node degree analysis were similar to those of the functional connectivity analysis. Our findings reveal for the first time that brain activity in the γ band may play a key role in the default mode network in cingulate gyrus epilepsy. Altered functional connectivity of the left angular gyrus and left posterior cingulate cortex may be a new biomarker for cingulate gyrus epilepsy.

Keywords: angular gyrus, cingulate gyrus epilepsy, default mode network, magnetoencephalography

Human brain mapping (2020), Vol. 41, No. 9 (32096905) (5 citations)

Scalp ripples as prognostic biomarkers of epileptogenicity in pediatric surgery (2020)

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OBJECTIVE To assess the ability of high-density Electroencephalography (HD-EEG) and magnetoencephalography (MEG) to localize interictal ripples, distinguish between ripples co-occurring with spikes (ripples-on-spike) and independent from spikes (ripples-alone), and evaluate their localizing value as biomarkers of epileptogenicity in children with medically refractory epilepsy.

METHODS We retrospectively studied 20 children who underwent epilepsy surgery. We identified ripples on HD-EEG and MEG data, localized their generators, and compared them with intracranial EEG (icEEG) ripples. When ripples and spikes co-occurred, we performed source imaging distinctly on the data above 80 Hz (to localize ripples) and below 70 Hz (to localize spikes). We assessed whether missed resection of ripple sources predicted poor outcome, separately for ripples-on-spikes and ripples-alone. Similarly, predictive value of spikes was calculated.

RESULTS We observed scalp ripples in 16 patients (10 good outcome). Ripple sources were highly concordant to the icEEG ripples (HD-EEG concordance: 79%; MEG: 83%). When ripples and spikes co-occurred, their sources were spatially distinct in 83-84% of the cases. Removing the sources of ripples-on-spikes predicted good outcome with 90% accuracy for HD-EEG ($P = 0.008$) and 86% for MEG ($P = 0.044$). Conversely, removing ripples-alone did not predict outcome. Resection of spike sources (generated at the same time as ripples) predicted good outcome for HD-EEG ($P = 0.036$; accuracy = 87%), while did not reach significance for MEG ($P = 0.1$; accuracy = 80%).

INTERPRETATION HD-EEG and MEG localize interictal ripples with high precision in children with refractory epilepsy. Scalp ripples-on-spikes are prognostic, noninvasive biomarkers of epileptogenicity, since removing their cortical generators predicts good outcome. Conversely, scalp ripples-alone are most likely generated by non-epileptogenic areas.

Annals of clinical and translational neurology (2020), Vol. 7, No. 3 (32096612) (22 citations)

Somatosensory evoked fields predict response to vagus nerve stimulation (2020)

Mithani, Karim; Wong, Simeon M; Mikhail, Mirriam; Pourmotabbed, Haatef; Pang, Elizabeth; Sharma, Roy; Yau, Ivanna; Ochi, Ayako; Otsubo, Hiroshi; Snead, O Carter; Donner, Elizabeth; Go, Cristina; Widjaja, Elysa; Babajani-Feremi, Abbas; Ibrahim, George M

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ABSTRACT There is an unmet need to develop robust predictive algorithms to preoperatively identify pediatric epilepsy patients who will respond to vagus nerve stimulation (VNS). Given the similarity in the neural circuitry between vagus and median nerve afferent projections to the primary somatosensory cortex, the current study hypothesized that median nerve somato-

sensory evoked field(s) (SEFs) could be used to predict seizure response to VNS. Retrospective data from forty-eight pediatric patients who underwent VNS at two different institutions were used in this study. Thirty-six patients ("Discovery Cohort") underwent preoperative electrical median nerve stimulation during magnetoencephalography (MEG) recordings and 12 patients ("Validation Cohort") underwent preoperative pneumatic stimulation during MEG. SEFs and their spatial deviation, waveform amplitude and latency, and event-related connectivity were calculated for all patients. A support vector machine (SVM) classifier was trained on the Discovery Cohort to differentiate responders from non-responders based on these input features and tested on the Validation Cohort by comparing the model-predicted response to VNS to the known response. We found that responders to VNS had significantly more widespread SEF localization and greater functional connectivity within limbic and sensorimotor networks in response to median nerve stimulation. No difference in SEF amplitude or latencies was observed between the two cohorts. The SVM classifier demonstrated 88.9% accuracy (0.93 area under the receiver operator characteristics curve) on cross-validation, which decreased to 67% in the Validation cohort. By leveraging overlapping neural circuitry, we found that median nerve SEF characteristics and functional connectivity could identify responders to VNS.

Keywords: Connectomics, Evoked potentials, Machine learning, SEF, VNS

NeuroImage. Clinical (2020), Vol. 26 (32070812) (13 citations)

QuPWM: Feature Extraction Method for Epileptic Spike Classification (2020)

Chahid, Abderrazak; Albalawi, Fahad; Alotaiby, Turky Nayef; Al-Hameed, Majed Hamad; Alshebeili, Saleh; Laleg-Kirati, Taous-Meriem

ABSTRACT Epilepsy is a neurological disorder ranked as the second most serious neurological disease known to humanity, after stroke. Inter-ictal spiking is an abnormal neuronal discharge after an epileptic seizure. This abnormal activity can originate from one or more cranial lobes, often travels from one lobe to another, and interferes with normal activity from the affected lobe. The common practice for Inter-ictal spike detection of brain signals is via visual scanning of the recordings, which is a subjective and a very time-consuming task. Motivated by that, this article focuses on using machine learning for epileptic spikes classification in magnetoencephalography (MEG) signals. First, we used the Position Weight Matrix (PWM) method combined with a uniform quantizer to generate useful features from time domain and frequency domain through a Fast Fourier Transform (FFT) of the framed raw MEG signals. Second, the extracted features are fed to standard classifiers for inter-ictel spikes classification. The proposed technique shows great potential in spike classification and reducing the feature vector size. Specifically, the proposed technique achieved average sensitivity up to 87% and specificity up to 97% using 5-folds cross-validation applied to a balanced dataset. These samples are extracted from nine epileptic subjects using a sliding frame of size 95 samples-points with a step-size of 8 sample-points.

IEEE journal of biomedical and health informatics (2020), Vol. 24, No. 10 (32054592) (4 citations)

A novel method for extracting interictal epileptiform discharges in multi-channel MEG: Use of fractional type of blind source separation (2020)

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OBJECTIVE Visual inspection of interictal epileptiform discharges (IEDs) in multi-channel MEG requires a time-consuming evaluation process and often leads to inconsistent results due to variability of IED waveforms.

Here, we propose a novel extraction method for IEDs using a T/k type of blind source separation (BSST/k).

METHODS We applied BSST/k with seven patients with focal epilepsy to test the accuracy of identification of IEDs. We conducted comparisons of the results of BSS components with those obtained by visual inspection in sensor-space analysis.

RESULTS BSST/k provided better signal estimation of IEDs compared with sensor-space analysis. Importantly, BSST/k was able to uncover IEDs that could not be detected by visual inspection. Furthermore, IED components were clearly extracted while preserving spike and wave morphology. Variable IED waveforms were decomposed into one dominant component.

CONCLUSIONS BSST/k was able to visualize the spreading signals over multiple channels into a single component from a single epileptogenic zone. BSST/k can be applied to focal epilepsy with a simple parameter setting.

SIGNIFICANCE Our novel method was able to highlight IEDs with increased accuracy for identification of IEDs from multi-channel MEG data.

Keywords: Blind source separation, Interictal epileptiform discharges, Magnetoencephalography, Time-delayed correlation

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 2 (31887614) (3 citations)

Altered effective connectivity network in patients with insular epilepsy: A high-frequency oscillations magnetoencephalography study (2020)

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OBJECTIVE The project aimed to determine the alterations in the effective connectivity (EC) neural network in patients with insular epilepsy based on interictal high-frequency oscillations (HFOs) from magnetoencephalography (MEG) data.

METHODS We studied MEG data from 22 insular epilepsy patients and 20 normal subjects. Alterations in spatial pattern and connection properties of the patients with insular epilepsy were investigated in the entire brain network and insula-based network.

RESULTS Analyses of the parameters of graph theory revealed the over-connectivity and small-world configuration of the global connectivity patterns observed in the patients. In the insula-based network, the insular cortex ipsilateral to the seizure onset displayed increased efferent and afferentEC. Left insular epilepsy featured strong connectivity with the bilateral hemispheres, whereas right insular epilepsy featured increased connectivity with only the ipsilateral hemisphere.

CONCLUSIONS Patients with insular epilepsy display alterations in the EC network in terms of both whole-brain connectivity and the insula-based network during interictal HFOs.

SIGNIFICANCE Alterations of interictal HFO-based networks provide evidence that epilepsy networks,

instead of epileptic foci, play a key role in the complex pathophysiological mechanisms of insular epilepsy. The dysfunction of HFO networks may prove to be a novel promising biomarker and the cause of interictal brain dysfunctions in insular epilepsy.

Keywords: Effective connectivity, Graph theory, Insular epilepsy, Magnetoencephalography, Ripples

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 2 (31865139) (10 citations)

EMS-Net: A Deep Learning Method for Autodetecting Epileptic Magnetoencephalography Spikes (2020)

Zheng, Li; Liao, Pan; Luo, Shen; Sheng, Jingwei; Teng, Pengfei; Luan, Guoming; Gao, Jia-Hong

ABSTRACT Epilepsy is a neurological disorder characterized by sudden and unpredictable epileptic seizures, which incurs significant negative impacts on patients' physical, psychological and social health. A practical approach to assist with the clinical assessment and treatment planning for patients is to process magnetoencephalography (MEG) data to identify epileptogenic zones. As a widely accepted biomarker of epileptic foci, epileptic MEG spikes need to be precisely detected. Given that the visual inspection of spikes is time consuming, an automatic and efficient system with adequate accuracy for spike detection is valuable in clinical practice. However, current approaches for MEG spike autodetection are dependent on hand-engineered features. Here, we propose a novel multiview Epileptic MEG Spikes detection algorithm based on a deep learning Network (EMS-Net) to accurately and efficiently recognize the spike events from MEG raw data. The results of the leave-k-subject-out validation tests for multiple datasets (i.e., balanced and realistic datasets) showed that EMS-Net achieved state-of-the-art classification performance (i.e., accuracy: 91.82% - 99.89%; precision: 91.90% - 99.45%; sensitivity: 91.61% - 99.53%; specificity: 91.60% - 99.96%; f1 score: 91.70% - 99.48%; and area under the curve: 0.9688 - 0.9998).

IEEE transactions on medical imaging (2020), Vol. 39, No. 6 (31831410) (10 citations)

The impact of MEG results on surgical outcomes in patients with drug-resistant epilepsy associated with focal encephalomalacia: a single-center experience (2020)

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PURPOSE To analyze the impact of magnetoencephalography (MEG) results on surgical outcomes in patients with drug-resistant epilepsy secondary to encephalomalacia.

METHODS We retrospectively reviewed 121 patients with drug-resistant epilepsy associated with encephalomalacia who underwent MEG followed by resection surgery. Patients were subdivided into concordant MEG group and dis-concordant MEG group for analysis based on whether the MEG results were in concordance with epileptogenic zones or not.

RESULTS 121 patients were included in the present study. The MEG spike sources of 73 (60.33%) patients were in concordance with epileptogenic zones while the MEG spike sources of the other 48 (39.67%) were in dis-concordance with epileptogenic zones. Favorable seizure outcomes were achieved in 79.45% (58 of 73) of patients with concordant MEG results while only 62.50% (30 of 48) of patients with dis-concordant MEG results were seizure free with a follow-up of 2-10 years. The differences of seizure-free rate between patients with concordant MEG results and dis-concordant MEG results were statistically significant. For patients with concordant MEG results, bilateral lesions on MRI are the only independent predictor of unfavorable seizure outcomes. For patients with discordant MEG results, duration of seizures is the only independent predictor of unfavorable seizure outcomes.

CONCLUSIONS Concordant MEG results are associated with favorable seizure outcomes. Bilateral lesions on MRI independently predict unfavorable seizure outcomes in patients with concordant MEG results while longer seizure durations independently predict unfavorable seizure outcomes in patients with discordant MEG results.

Keywords: Drug-resistant epilepsy, Epilepsy surgery, Epileptogenic zone, Magnetoencephalography

Journal of neurology (2020), Vol. 267, No. 3 (31773245) (3 citations)

Migraine

Resting-state magnetoencephalographic oscillatory connectivity to identify patients with chronic migraine using machine learning (2022)

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ABSTRACT To identify and validate the neural signatures of resting-state oscillatory connectivity for chronic migraine (CM), we used machine learning techniques to classify patients with CM from healthy controls (HC) and patients with other pain disorders. The cross-sectional study obtained resting-state magnetoencephalographic data from 240 participants (70 HC, 100 CM, 35 episodic migraine [EM], and 35 fibromyalgia [FM]). Source-based oscillatory connectivity of relevant cortical regions was calculated to determine intrinsic connectivity at 1-40 Hz. A classification model that employed a support vector machine was developed using the magnetoencephalographic data to assess the reliability and generalizability of CM identification. In the findings, the discriminative features that differentiate CM from HC were principally observed from the functional interactions between salience, sensorimotor, and part of the default mode networks. The classification model with these features exhibited excellent performance in distinguishing patients with CM from HC (accuracy ≥ 86.8%, area under the curve (AUC) ≥ 0.9) and from those with EM (accuracy: 94.5%, AUC: 0.96). The model also achieved high performance (accuracy: 89.1%, AUC: 0.91) in classifying CM from other pain disorders (FM in this study). These resting-state magnetoencephalographic electrophysiological features yield oscillatory connectivity to identify patients with CM from those with a different type of migraine and pain disorder, with adequate reliability and generalizability.

Keywords: Chronic migraine, Machine learning, Magnetoencephalography, Pain disorders, Resting-state oscillatory connectivity

The journal of headache and pain (2022), Vol. 23, No. 1 (36192689) (0 citations)

Headache-related circuits and high frequencies evaluated by EEG, MRI, PET as potential biomarkers to differentiate chronic and episodic migraine: Evidence from a systematic review (2022)

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BACKGROUND The diagnosis of migraine is mainly clinical and self-reported, which makes additional examinations unnecessary in most cases. Migraine can be subtyped into chronic (CM) and episodic (EM). Despite the very high prevalence of migraine, there are no evidence-based guidelines for differentiating between these subtypes other than the number of days of migraine headache per month. Thus, we consider it timely to perform a systematic review to search for physiologi-

cal evidence from functional activity (as opposed to anatomical structure) for the differentiation between CM and EM, as well as potential functional biomarkers. For this purpose, Web of Science (WoS), Scopus, and PubMed databases were screened.

FINDINGS Among the 24 studies included in this review, most of them (22) reported statistically significant differences between the groups of CM and EM. This finding is consistent regardless of brain activity acquisition modality, ictal stage, and recording condition for a wide variety of analyses. That speaks for a supramodal and domain-general differences between CM and EM that goes beyond a differentiation based on the days of migraine per month. Together, the reviewed studies demonstrates that electro- and magneto-physiological brain activity (M/EEG), as well as neurovascular and metabolic recordings from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), show characteristic patterns that allow to differentiate between CM and EM groups.

CONCLUSIONS Although a clear brain activity-based biomarker has not yet been identified to distinguish these subtypes of migraine, research is approaching headache specialists to a migraine diagnosis based not only on symptoms and signs reported by patients. Future studies based on M/EEG should pay special attention to the brain activity in medium and fast frequency bands, mainly the beta band. On the other hand, fMRI and PET studies should focus on neural circuits and regions related to pain and emotional processing.

Keywords: Chronic migraine (CM), Electroencephalography (EEG), Episodic migraine (EM), Functional activity, Functional magnetic resonance imaging (fMRI), Magnetoencephalography (MEG), Positron emission tomography (PET)

The journal of headache and pain (2022), Vol. 23, No. 1 (35927625) (1 citation)

Altered effective connectivity in migraine patients during emotional stimuli: a multi-frequency magnetoencephalography study (2022)

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BACKGROUND Migraine is a common and disabling primary headache, which is associated with a wide range of psychiatric comorbidities. However, the mechanisms of emotion processing in migraine are not fully understood yet. The present study aimed to investigate the neural network during neutral, positive, and negative emotional stimuli in the migraine patients.

METHODS A total of 24 migraine patients and 24 age- and sex-matching healthy controls were enrolled in this study. Neuromagnetic brain activity was recorded using a whole-head magnetoencephalography (MEG) system upon exposure to human facial expression stimuli. MEG data were analyzed in multi-frequency ranges from 1 to 100 Hz.

RESULTS The migraine patients exhibited a significant enhancement in the effective connectivity from the prefrontal lobe to the temporal cortex during the negative emotional stimuli in the gamma frequency (30-90 Hz). Graph theory analysis revealed that the migraine patients had an increased degree and clustering coefficient of connectivity in the delta frequency range (1-4 Hz) upon exposure to positive emotional stimuli and an increased degree of connectivity in the delta frequency range (1-4 Hz) upon exposure to negative emotional stimuli. Clinical correlation analysis showed that the history, attack frequency, duration, and neuropsychological scales of the migraine patients had a

negative correlation with the network parameters in certain frequency ranges.

CONCLUSIONS The results suggested that the individuals with migraine showed deviant effective connectivity in viewing the human facial expressions in multi-frequencies. The prefrontal-temporal pathway might be related to the altered negative emotional modulation in migraine. These findings suggested that migraine might be characterized by more universal altered cerebral processing of negative stimuli. Since the significant result in this study was frequency-specific, more independent replicative studies are needed to confirm these results, and to elucidate the neurocircuitry underlying the association between migraine and emotional conditions.

Keywords: Effective connectivity, Emotional stimuli, Magnetoencephalography, Migraine, Multi-frequency

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Migraine chronification is associated with beta-band connectivity within the pain-related cortical regions: a magnetoencephalographic study (2021)

Hsiao, Fu-Jung; Chen, Wei-Ta; Liu, Hung-Yu; Wang, Yen-Feng; Chen, Shih-Pin; Lai, Kuan-Lin; Hope Pan, Li-Ling; Coppola, Gianluca; Wang, Shuu-Jiun

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ABSTRACT Pain disorders are associated with aberrant oscillations in the pain-related cortical regions; however, few studies have investigated the relationship between the functional cortical network and migraine chronification through direct neural signals. Magnetoencephalography was used to record the resting-state brain activity of healthy controls as well as patients with episodic migraine (EM) and chronic migraine (CM). The source-based oscillatory dynamics of the pain-related cortical regions, which comprises 10 node regions (the bilateral primary [SI] and secondary somatosensory cortices, insula, medial frontal cortex, and anterior cingulate cortex [ACC]), were calculated to determine the intrinsic connectivity and node strength at 1 to 40 Hz. The total node strength within the pain-related cortical regions was smaller in the beta band in patients with migraine (70 EM and 80 CM) than in controls (n = 65). In the beta band, the node strength and functional connectivity values of patients with CM and patients with EM differed from those of controls in specific cortical areas, notably the left SI (EM < control) and bilateral ACC (CM < control); moreover, the node strength was lower in patients with CM than in those with EM. In all patients with migraine, negative correlations were observed between headache frequency and node strength in the bilateral ACC. In conclusion, migraine is characterized by reduced beta oscillatory connectivity within the pain-related cortical regions. Reduced beta connectivity in the ACC is linked to migraine chronification. Longitudinal studies should verify whether this oscillation change is a brain signature and a potential neuromodulation target for migraine.

Pain (2021), Vol. 162, No. 10 (34534180) (6 citations)

Brain Excitability in Tension-Type Headache: a Separate Entity from Migraine? (2021)

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PURPOSE OF REVIEW Tension-type headache is often regarded as the "normal" headache due to its high prevalence and mild disability in contrast with migraine. Clinically, both headaches are common comorbidities to each other. To date there has been many studies linked migraine to a brain excitability disorder. This review summarized earlier studies on brain excitability of TTH and discuss if TTH is a separate clinical

entity from migraine as suggested by the diagnostic criteria.

RECENT FINDINGS A recent magnetoencephalographic study from our group enrolled patients with "strict-criteria" TTH (i.e., absence of any migraine characteristics and associated symptoms) to compare the somatosensory excitability with patients with migraine and controls. This study provided evidence that TTH and migraine differ in excitability profiles and the measurement of preactivation excitability was able to discriminate TTH from migraine. Earlier studies on brain excitability of TTH yielded negative findings or a common change shared with migraine. Future studies using strict diagnostic criteria to avoid the unwanted interference from migraine comorbidity may help decipher the "true" pathophysiology of TTH, which may pave the way to a TTH-specific brain signature and treatment.

Keywords: Brain excitability, Magnetoencephalography (MEG), Migraine, Neurophysiology, Somatosensory gating, Tension-type headache (TTH)

Current pain and headache reports (2021), Vol. 24, No. 12 (33415543) (1 citation)

Individual pain sensitivity is associated with resting-state cortical activities in healthy individuals but not in patients with migraine: a magnetoencephalography study (2020)

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BACKGROUND Pain sensitivity may determine the risk, severity, prognosis, and efficacy of treatment of clinical pain. Magnetic resonance imaging studies have linked thermal pain sensitivity to changes in brain structure. However, the neural correlates of mechanical pain sensitivity remain to be clarified through investigation of direct neural activities on the resting-state cortical oscillation and synchrony.

METHODS We recorded the resting-state magnetoencephalographic (MEG) activities of 27 healthy individuals and 30 patients with episodic migraine (EM) and analyzed the source-based oscillatory powers and functional connectivity at 2 to 59 Hz in pain-related cortical regions, which are the bilateral anterior cingulate cortex (ACC), medial orbitofrontal (MOF) cortex, lateral orbitofrontal (LOF) cortex, insula cortex, primary somatosensory cortex (SI), primary motor cortex (MI), and posterior cingulate cortex (PCC). The mechanical punctate pain threshold (MPPT) was obtained at the supraorbital area (the first branch of the trigeminal nerve dermatome, V1) and the forearm (the first thoracic nerve dermatome, T1) and further correlated with MEG measures.

RESULTS The MPPT is inversely correlated with the resting-state relative powers of gamma oscillation in healthy individuals (all corrected $P < 0.05$). Specifically, inverse correlation was noted between the MPPT at V1 and gamma powers in the bilateral insula ($r = -0.592$ [left] and -0.529 [right]), PCC ($r = -0.619$ and -0.541) and MI ($r = -0.497$ and -0.549) and between the MPPT at T1 and powers in the left PCC ($r = -0.561$) and bilateral MI ($r = -0.509$ and -0.520). Furthermore, resting-state functional connectivity at the delta to beta bands, especially between frontal (MOF, ACC, LOF, and MI), parietal (PCC), and sensorimotor (bilateral SI and MI) regions, showed a positive correlation with the MPPT at V1 and T1 (all corrected $P < 0.05$). By contrast, in patients with EM, the MPPT was not associated with resting-state cortical activities.

CONCLUSIONS Pain sensitivity in healthy individuals is associated with the resting-state gamma oscillation and functional connectivity in pain-related cortical regions. Further studies must be conducted in a large population to confirm whether resting-state cortical activities can be an objective measurement of pain sensitivity in individuals without clinical pain.

Keywords: Episodic migraine, Functional connectivity, Gamma, Magnetoencephalography, Oscillation, Pain sensitivity, Resting state

The journal of headache and pain (2020), Vol. 21, No. 1 (33198621) (5 citations)

Auditory attention alterations in migraine: A behavioral and MEG/EEG study (2020)

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OBJECTIVES To evaluate alterations of top-down and/or bottom-up attention in migraine and their cortical underpinnings.

METHODS 19 migraineurs between attacks and 19 matched control participants performed a task evaluating jointly top-down and bottom-up attention, using visually-cued target sounds and unexpected task-irrelevant distracting sounds. Behavioral responses and magneto- and electro-encephalography signals were recorded. Event-related potentials and fields were processed and source reconstruction was applied to event-related fields.

RESULTS At the behavioral level, neither top-down nor bottom-up attentional processes appeared to be altered in migraine. However, migraineurs presented heightened evoked responses following distracting sounds (orienting component of the N1 and Re-Orienting Negativity, RON) and following target sounds (orienting component of the N1), concomitant to an increased recruitment of the right temporo-parietal junction. They also displayed an increased effect of the cue informational value on target processing resulting in the elicitation of a negative difference (Nd).

CONCLUSIONS Migraineurs appear to display increased bottom-up orienting response to all incoming sounds, and an enhanced recruitment of top-down attention.

SIGNIFICANCE The interictal state in migraine is characterized by an exacerbation of the orienting response to attended and unattended sounds. These attentional alterations might participate to the peculiar vulnerability of the migraine brain to all incoming stimuli.

Keywords: Bottom-up attention, Electroencephalography, Event-related responses, Magnetoencephalography, Migraine, Top-down attention

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 8 (32619799) (4 citations)

Fading of brain network fingerprint in Parkinson's disease predicts motor clinical impairment (2023)

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ABSTRACT The clinical connectome fingerprint (CCF) was recently introduced as a way to assess brain dynamics. It is an approach able to recognize individuals, based on the brain network. It showed its applicability providing network features used to predict the cognitive decline in preclinical Alzheimer's disease. In this article, we explore the performance of CCF in 47 Parkinson's disease (PD) patients and 47 healthy controls, under the hypothesis that patients would show reduced identifiability as compared to controls, and that such reduction could be used to predict motor impairment. We used source-reconstructed magnetoencephalography signals to build two functional connectomes for 47 patients with PD and 47 healthy controls. Then, exploiting the two connectomes per individual, we investigated the identifiability characteristics of each subject in each group. We observed reduced identifiability in patients compared to healthy individuals in the beta band. Furthermore, we found that the reduction in identifiability was proportional to the motor impairment, assessed through the Unified Parkinson's Disease Rating Scale, and, interestingly, able to predict it (at the subject level), through a cross-validated regression model. Along with previous evidence, this article shows that CCF captures disrupted dynamics in neurodegenerative diseases and is particularly effective in predicting motor clinical impairment in PD.

Keywords: Parkinson's disease, brain fingerprint, brain network, clinical connectome fingerprint, magnetoencephalography, motor impairment, neurodegenerative disease

Human brain mapping (2023), Vol. 44, No. 3 (36413043) (1 citation)

Neurophysiological Basis of Deep Brain Stimulation and Botulinum Neurotoxin Injection for Treating Oromandibular Dystonia (2022)

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ABSTRACT Oromandibular dystonia (OMD) induces severe motor impairments, such as masticatory disturbances, dysphagia, and dysarthria, resulting in a serious decline in quality of life. Non-invasive brain-imaging techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) are powerful approaches that can elucidate human cortical activity with high temporal resolution. Previous studies with EEG and MEG have revealed that movements in the stomatognathic system are regulated by the bilateral

central cortex. Recently, in addition to the standard therapy of botulinum neurotoxin (BoNT) injection into the affected muscles, bilateral deep brain stimulation (DBS) has been applied for the treatment of OMD. However, some patients' OMD symptoms do not improve sufficiently after DBS, and they require additional BoNT therapy. In this review, we provide an overview of the unique central spatiotemporal processing mechanisms in these regions in the bilateral cortex using EEG and MEG, as they relate to the sensorimotor functions of the stomatognathic system. Increased knowledge regarding the neurophysiological underpinnings of the stomatognathic system will improve our understanding of OMD and other movement disorders, as well as aid the development of potential novel approaches such as combination treatment with BoNT injection and DBS or non-invasive cortical current stimulation therapies.

Keywords: botulinum neurotoxin, deep brain stimulation, electroencephalography, globus pallidus, magnetoencephalography, motor function, oromandibular dystonia, sensorimotor function, stomatognathic function

Toxins (2022), Vol. 14, No. 11 (36356002) (0 citations)

Insights from Magnetic Evoked Field Analysis in Patients with Wilson's Disease (2022)

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AIMS To study the latency, amplitude, and source localization of magnetic evoked field (MEF) responses to visual, auditory, and somatosensory stimuli in Wilson's disease (WD) using magnetoencephalography (MEG) and compare it with "healthy" controls, and correlate the observations with disease severity and brain MRI.

METHODS MEF of 28 patients with neurological WD (age: 22.82 ± 5.8 years; M:F = 12:16) and 21 matched controls (age: 25.0 ± 4.6 years; M:F = 10:11) were recorded using MEG. Source localization was performed using standard models on the components of M100, M20, and M100 for visual, somatosensory, and auditory evoked fields, respectively and its latency/amplitude was correlated with disease severity.

RESULTS There were significant differences in source location between control and WD during visual evoked field (VEF) and auditory evoked field (AEF) studies. Latencies of M20 (right-p = 0.02; left-p = 0.04) and M32 (right-p = 0.01) components of SSEF were significantly prolonged. The amplitude of M20 was significantly reduced in patients bilaterally (P = 0.001). There was a trend for the prolonged latency of M100 of VEF in patients (P = 0.09). Five patients had reduced right M145 compared to 8 controls. The left somatosensory evoked fields (SSEF) latency correlated with disease severity (P = 0.04). There was no significant correlation between major components of other MEF with disease severity or MRI score.

CONCLUSIONS This study, first of its kind to use MEF analysis in a large cohort of patients with WD, detected subclinical but a variable degree of abnormalities, most consistently of SSEF. It provides valuable insights of functioning and localization of various pathways in a disease known to have protean clinical manifestations and widespread MRI changes.

Keywords: AEF, MEG, SSEF, VEF, Wilson's disease

Neurology India (2022), Vol. 70, No. 5 (36352595) (0 citations)

Functional connectivity maps of theta/alpha and beta coherence within the subthalamic nucleus region (2022)

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ABSTRACT The subthalamic nucleus (STN) is a primary target for deep brain stimulation in Parkinson's disease (PD). Although small in size, the STN is commonly partitioned into sensorimotor, cognitive/associative, and limbic subregions based on its structural connectivity profile to cortical areas. We investigated whether such a regional specialization is also supported by functional connectivity between local field potential recordings and simultaneous magnetoencephalography. Using a novel data set of 21 PD patients, we replicated previously reported cortico-STN coherence networks in the theta/alpha and beta frequency ranges, and looked for the spatial distribution of these networks within the STN region. Although theta/alpha and beta coherence peaks were both observed in on-medication recordings from electrode contacts at several locations within and around the STN, sites with theta/alpha coherence peaks were situated at significantly more inferior MNI coordinates than beta coherence peaks. Sites with only theta/alpha coherence peaks, i.e. without distinct beta coherence, were mostly located near the border of sensorimotor and cognitive/associative subregions as defined by a tractography-based atlas of the STN. Peak coherence values were largely unaltered by the medication state of the subject, however, theta/alpha peaks were more often identified in recordings obtained after administration of dopaminergic medication. Our findings suggest the existence of a frequency-specific topography of cortico-STN coherence within the STN, albeit with considerable spatial overlap between functional networks. Consequently, optimization of deep brain stimulation targeting might remain a trade-off between alleviating motor symptoms and avoiding adverse neuropsychiatric side effects.

Keywords: Deep brain stimulation, Functional connectivity, Magnetoencephalography, Parkinson's disease, Subthalamic nucleus

NeuroImage (2022), Vol. 257 (35580809) (0 citations)

Cortical beta burst dynamics are altered in Parkinson's disease but normalized by deep brain stimulation (2022)

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ABSTRACT Exaggerated subthalamic beta oscillatory activity and increased beta range cortico-subthalamic synchrony have crystallized as the electrophysiological hallmarks of Parkinson's disease. Beta oscillatory activity is not tonic but occurs in 'bursts' of transient amplitude increases. In Parkinson's disease, the characteristics of these bursts are altered especially in the basal ganglia. However, beta oscillatory dynamics at the cortical level and how they compare with healthy brain activity is less well studied. We used magnetoencephalography (MEG) to study sensorimotor cortical beta bursting and its modulation by subthalamic deep brain stimulation in Parkinson's disease patients and age-matched healthy controls. We show that the changes in beta bursting amplitude and duration typical of Parkinson's disease can also be observed in the sensorimotor cortex, and that they are modulated by chronic subthalamic deep brain stimulation, which, in turn, is reflected in improved motor function at the behavioural level. In addition to the changes in individual beta bursts, their timing relative to each other was altered in patients compared to controls: bursts were more clustered in untreated Parkinson's disease, occurring in 'bursts of bursts', and re-burst probability was higher for longer compared to shorter bursts. During active deep brain stimulation, the beta bursting in patients resembled healthy controls' data. In summary, both individual bursts' characteristics and burst patterning are affected in Parkinson's disease, and subthalamic deep brain stimulation normalizes some of these changes to resemble healthy controls' beta bursting activity, suggesting a non-invasive biomarker for patient and treatment follow-up.

Keywords: Beta burst, Deep brain stimulation, Magnetoencephalography, Oscillatory activity, Parkinson's disease, Resting state

NeuroImage (2022), Vol. 257 (35569783) (2 citations)

Neuronal oscillations predict deep brain stimulation outcome in Parkinson's disease (2022)

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BACKGROUND Neuronal oscillations are linked to symptoms of Parkinson's disease. This relation can be exploited for optimizing deep brain stimulation (DBS), e.g. by informing a device or human about the optimal location, time and intensity of stimulation. Whether oscillations predict individual DBS outcome is not clear so far.

OBJECTIVE To predict motor symptom improvement from subthalamic power and subthalamo-cortical coherence.

METHODS We applied machine learning techniques to simultaneously recorded magnetoencephalography and local field potential data from 36 patients with

Parkinson's disease. Gradient-boosted tree learning was applied in combination with feature importance analysis to generate and understand out-of-sample predictions.

RESULTS A few features sufficed for making accurate predictions. A model operating on five coherence features, for example, achieved correlations of r > 0.8 between actual and predicted outcomes. Coherence comprised more information in less features than subthalamic power, although in general their information content was comparable. Both signals predicted akinesia/rigidity reduction best. The most important local feature was subthalamic high-beta power (20-35 Hz). The most important connectivity features were subthalamo-parietal coherence in the very high frequency band (>200 Hz) and subthalamo-parietal coherence in low-gamma band (36-60 Hz). Successful prediction was not due to the model inferring distance to target or symptom severity from neuronal oscillations.

CONCLUSION This study demonstrates for the first time that neuronal oscillations are predictive of DBS outcome. Coherence between subthalamic and parietal oscillations are particularly informative. These results highlight the clinical relevance of inter-areal synchrony in basal ganglia-cortex loops and might facilitate further improvements of DBS in the future.

Keywords: Deep brain stimulation, Machine learning, Neuronal oscillations, Parkinson's disease, Subthalamic nucleus

Brain stimulation (2022), Vol. 15, No. 3 (35568311) (2 citations)

Modulation of sensory cortical activity by deep brain stimulation in advanced Parkinson's disease (2022)

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ABSTRACT Despite optimal oral drug treatment, about 90% of patients with Parkinson's disease develop motor fluctuation and dyskinesia within 5-10 years from the diagnosis. Moreover, the patients show non-motor symptoms in different sensory domains. Bilateral deep brain stimulation (DBS) applied to the subthalamic nucleus is considered the most effective treatment in advanced Parkinson's disease, and it has been suggested to affect sensorimotor modulation and relate to motor improvement in patients. However, observations on the relationship between sensorimotor activity and clinical improvement have remained sparse. Here, we studied the somatosensory evoked magnetic fields in 13 right-handed patients with advanced Parkinson's disease before and 7 months after stimulator implantation. Somatosensory processing was addressed with magnetoencephalography during alternated median nerve stimulation at both wrists. The strengths and the latencies of the ~60-ms responses at the contralateral primary somatosensory cortices were highly variable but detectable and reliably localized in all patients. The response strengths did not differ between preoperative and postoperative DBSON measurements. The change in the response strength between preoperative and postoperative condition in the dominant left hemisphere of our right-handed patients correlated with the alleviation of their motor symptoms ($p = .04$). However, the result did not survive correction for multiple comparisons. Magnetoencephalography appears an effective tool to explore non-motor effects in patients with Parkinson's disease, and it may help in understanding the neurophysiological basis of DBS. However, the high interindividual variability in the somatosensory responses and poor tolerability of DBSOFF condition warrants larger patient groups and measurements also in non-medicated patients.

Keywords: Parkinson's disease, deep brain stimulation, magnetoencephalography, non-motor cerebral activity, somatosensory processing

The European journal of neuroscience (2022), Vol. 56, No. 2 (35560964) (1 citation)

Conflict Detection in a Sequential Decision Task Is Associated with Increased Cortico-Subthalamic Coherence and Prolonged Subthalamic Oscillatory Response in the β Band (2022)

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ABSTRACT Making accurate decisions often involves the integration of current and past evidence. Here, we examine the neural correlates of conflict and evidence integration during sequential decision-making. Female and male human patients implanted with deep-brain stimulation (DBS) electrodes and age-matched and gender-matched healthy controls performed an expanded judgment task, in which they were free to choose how many cues to sample. Behaviorally, we found that while patients sampled numerically more cues, they were less able to integrate evidence and showed suboptimal performance. Using recordings of magnetoencephalography (MEG) and local field potentials (LFPs; in patients) in the subthalamic nucleus (STN), we found that β oscillations signaled conflict between cues within a sequence. Following cues that differed from previous cues, β power in the STN and cortex first decreased and then increased. Importantly, the conflict signal in the STN outlasted the cortical one, carrying over to the next cue in the sequence. Furthermore, after a conflict, there was an increase in coherence between the dorsal premotor cortex and STN in the β band. These results extend our understanding of cortico-subcortical dynamics of conflict processing, and do so in a context where evidence must be accumulated in discrete steps, much like in real life. Thus, the present work leads to a more nuanced picture of conflict monitoring systems in the brain and potential changes because of disease.SIGNIFICANCE STATEMENT Decision-making often involves the integration of multiple pieces of information over time to make accurate predictions. We simultaneously recorded whole-head magnetoencephalography (MEG) and local field potentials (LFPs) from the human subthalamic nucleus (STN) in a novel task which required integrating sequentially presented pieces of evidence. Our key finding is prolonged β oscillations in the STN, with a concurrent increase in communication with frontal cortex, when presented with conflicting information. These neural effects reflect the behavioral profile of reduced tendency to respond after conflict, as well as relate to suboptimal cue integration in patients, which may be directly linked to clinically reported side-effects of deep-brain stimulation (DBS) such as impaired decision-making and impulsivity.

Keywords: DBS, coherence, conflict, dorsal premotor cortex, evidence integration, human, subthalamic nucleus

The Journal of neuroscience: the official journal of the Society for Neuroscience (2022), Vol. 42, No. 23 (35501153) (1 citation)

Cortical oscillatory dysfunction in Parkinson disease during movement activation and inhibition (2022)

Disbrow, Elizabeth A; Glassy, Nathaniel D; Dressler, Elizabeth M; Russo, Kimberley; Franz, Elizabeth A; Turner, Robert S; Ventura, Maria I; Hinkley, Leighton; Zweig, Richard; Nagarajan, Srikantan S; Ledbetter, Christina R; Sigvardt, Karen A

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ABSTRACT Response activation and inhibition are functions fundamental to executive control that are disrupted in Parkinson disease (PD). We used magnetoencephalography to examine event related changes in oscillatory power amplitude, peak latency and frequency in cortical networks subserving these functions and identified abnormalities associated with PD. Participants (N = 18 PD, 18 control) performed a cue/target task that required initiation of an un-cued movement (activation) or inhibition of a cued movement. Reaction times were variable but similar across groups. Task related responses in gamma, alpha, and beta power were found across cortical networks including motor cortex, supplementary and pre- supplementary motor cortex, posterior parietal cortex, prefrontal cortex and anterior cingulate. PD-related changes in power and latency were noted most frequently in the beta band, however, abnormal power and delayed peak latency in the alpha band in the pre-supplementary motor area was suggestive of a compensatory mechanism. PD peak power was delayed in pre-supplementary motor area, motor cortex, and medial frontal gyrus only for activation, which is consistent with deficits in un-cued (as opposed to cued) movement initiation characteristic of PD.

PloS one (2022), Vol. 17, No. 3 (35245294) (0 citations)

Deep brain stimulation of subthalamic nucleus modulates cortical auditory processing in advanced Parkinson's Disease (2022)

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ABSTRACT Deep brain stimulation (DBS) has proven its clinical efficacy in Parkinson's disease (PD), but its exact mechanisms and cortical effects continue to be unclear. Subthalamic (STN) DBS acutely modifies auditory evoked responses, but its long-term effect on auditory cortical processing remains ambiguous. We studied with magnetoencephalography the effect of long-term STN DBS on auditory processing in patients with advanced PD. DBS resulted in significantly increased contra-ipsilateral auditory response latency difference at ~100 ms after stimulus onset compared with preoperative state. The effect is likely due to normalization of neuronal asynchrony in the auditory pathways. The present results indicate that STN DBS in advanced PD patients has long-lasting effects on cortical areas outside those confined to motor processing. Whole-head magnetoencephalography provides a feasible tool to study motor and non-motor neural networks in PD, and to track possible changes related to cortical reorganization or plasticity induced by DBS.

PloS one (2022), Vol. 17, No. 2 (35202426) (1 citation)

Deep brain stimulation for parkinson's disease induces spontaneous cortical hypersynchrony in extended motor and cognitive networks (2022)

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ABSTRACT The mechanism of action of deep brain stimulation (DBS) to the basal ganglia for Parkinson's disease remains unclear. Studies have shown that DBS decreases pathological beta hypersynchrony between the basal ganglia and motor cortex. However, little is known about DBS's effects on long range corticocortical synchronization. Here, we use machine learning combined with graph theory to compare resting-state cortical connectivity between the off and on-stimulation states and to healthy controls. We found that turning DBS on increased high beta and gamma band synchrony (26 to 50 Hz) in a cortical circuit spanning the motor, occipitoparietal, middle temporal, and prefrontal cortices. The synchrony in this network was greater in DBS on relative to both DBS off and controls, with no significant difference between DBS off and controls. Turning DBS on also increased network efficiency and strength and subnetwork modularity relative to both DBS off and controls in the beta and gamma band. Thus, unlike DBS's subcortical normalization of pathological basal ganglia activity, it introduces greater synchrony relative to healthy controls in cortical circuitry that includes both motor and non-motor systems. This increased high beta/gamma synchronization may reflect compensatory mechanisms related to DBS's clinical benefits, as well as undesirable non-motor side effects.

Keywords: deep brain stimulation, functional connectivity, magnetoencephalography, parkinson’s disease, synchrony

Cerebral cortex (New York, N.Y.: 1991) (2022), Vol. 32, No. 20 (35136991) (0 citations)

Magnetoencephalography detects phase-amplitude coupling in Parkinson's disease (2022)

Tanaka, Masataka; Yanagisawa, Takufumi; Fukuma, Ryohei; Tani, Naoki; Oshino, Satoru; Mihara, Masahito; Hattori, Noriaki; Kajiyama, Yuta; Hashimoto, Ryota; Ikeda, Manabu; Mochizuki, Hideki; Kishima, Haruhiko

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ABSTRACT To characterize Parkinson's disease, abnormal phase-amplitude coupling is assessed in the cortico-basal circuit using invasive recordings. It is unknown whether the same phenomenon might be found in regions other than the cortico-basal ganglia circuit. We hypothesized that using magnetoencephalography to assess phase-amplitude coupling in the whole brain can characterize Parkinson's disease. We recorded resting-state magnetoencephalographic signals in patients with Parkinson's disease and in healthy age- and sex-matched participants. We compared whole-brain signals from the two groups, evaluating the power spectra of 3 frequency bands (alpha, 8-12 Hz; beta, 13-25 Hz; gamma, 50-100 Hz) and the coupling between gamma amplitude and alpha or beta phases. Patients with Parkinson's disease showed significant beta-gamma phase-amplitude coupling that was widely distributed in the sensorimotor, occipital, and temporal cortices; healthy participants showed such coupling only in parts of the somatosensory and temporal cortices. Moreover, beta- and gamma-band power differed significantly between participants in the two groups ($P < 0.05$). Finally, beta-gamma phase-amplitude coupling in the sensorimotor cortices correlated significantly with motor symptoms of Parkinson's disease ($P < 0.05$); beta- and gamma-band power did not. We thus demonstrated that beta-gamma phase-amplitude coupling in the resting state characterizes Parkinson's disease.

Scientific reports (2022), Vol. 12, No. 1 (35115607) (2 citations)

Neural correlates of impaired response inhibition in the antisaccade task in Parkinson's disease (2022)

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ABSTRACT Deficits in response inhibition are a central feature of the highly prevalent dysexecutive syndrome found in Parkinson's disease (PD). Such deficits are related to a range of common clinically relevant symptoms including cognitive impairment as well as impulsive and compulsive behaviors. In this study, we explored the cortical dynamics underlying response inhibition during the mental preparation for the antisaccade task by recording magnetoencephalography (MEG) and eye-movements in 21 non-demented patients with early to mid-stage Parkinson's disease and 21 age-matched healthy control participants (HC). During the pre-stimulus preparatory period for antisaccades we observed: Taken together, the results indicate that alterations in pre-stimulus prefrontal alpha and beta activity hinder proactive response inhibition and in turn result in higher error rates and prolonged response latencies in PD.

Keywords: Antisaccade, Executive function, Eye-tracking, Impulsivity, Inhibition control, Parkinson's disease

Behavioural brain research (2022), Vol. 422 (35063499) (0 citations)

Profiling Parkinson's disease cognitive phenotypes via resting-state magnetoencephalography (2022)

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ABSTRACT Aberrant brain oscillations are a hallmark of Parkinson's disease (PD) pathophysiology and may be related to both motor and nonmotor symptoms. Mild cognitive impairment (MCI) affects many people with PD even at the time of diagnosis and conversion risks to PD dementia (PDD) are very high. Unfortunately, pharmacotherapies are not addressing cognitive symptoms in PD. Profiling PD cognitive phenotypes (e.g., MCI, PDD, etc.) may therefore help inform future treatments. Neurophysiological methods, such as magnetoencephalography (MEG), offer the advantage of observing oscillatory patterns, whose regional and temporal profiles may elucidate how cognitive changes relate to neural mechanisms. We conducted a resting-state MEG cross-sectional study of 89 persons with PD stratified into three phenotypic groups: normal cognition, MCI, and PDD, to identify brain regions and frequencies most associated with each cognitive profile. In addition, a neuropsychological battery was administered to assess each domain of cognition. Our data showed higher power in lower frequency bands (delta and theta) observed along with more severe cognitive impairment and associated with memory, language, attention, and global cognition. Of the total 119 brain parcels assessed during source analysis, widespread group differences were found in the beta band, with significant changes mostly occurring between the normal cognition and MCI groups. Moreover, bilateral frontal and left-hemispheric regions were particularly affected in the other frequencies as cognitive decline becomes more pronounced. Our results suggest that MCI and PDD may be qualitatively distinct cognitive phenotypes, and most dramatic changes seem to have happened when the PD brain shows mild cognitive decline.NEW & NOTEWORTHY Can we better stage cognitive decline in patients with Parkinson's disease (PD)? Here, we provide evidence that mild cognitive impairment, rather than being simply a milder form of dementia, may be a qualitatively distinct phase in its development. We suggest that the most dramatic neurophysiological changes may occur during the time the PD brain transitions from normal cognition to MCI, then compensatory changes further occur as the brain "switches" to a dementia state.

Keywords: Parkinson's, beamforming, cognitive impairment, magnetoencephalography, resting-state

Journal of neurophysiology (2022), Vol. 127, No. 1 (34936515) (0 citations)

Altered neural oscillations during complex sequential movements in patients with Parkinson's disease (2021)

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ABSTRACT The sequelae of Parkinson's disease (PD) includes both motor- and cognitive-related symptoms. Although traditionally considered a subcortical disease, there is increasing evidence that PD has a major impact on cortical function as well. Prior studies have reported alterations in cortical neural function in patients with PD during movement, but to date such studies have not examined whether the complexity of multicomponent movements modulate these alterations. In this study, 23 patients with PD (medication "off" state) and 27 matched healthy controls performed simple and complex finger tapping sequences during magnetoencephalography (MEG), and the resulting MEG data were imaged to identify the cortical oscillatory dynamics serving motor performance. The patients with PD were significantly slower than controls at executing the sequences overall, and both groups took longer to complete the complex sequences than the simple. In terms of neural differences, patients also exhibited weaker beta complexity-related effects in the right medial frontal gyrus and weaker complexity-related alpha activity in the right posterior and inferior parietal lobules, suggesting impaired motor sequence execution. Characterizing the cortical pathophysiology of PD could inform current and future therapeutic interventions that address both motor and cognitive symptoms.

Keywords: Alpha oscillations, Magnetoencephalography, Motor complexity, Parietal cortex

NeuroImage. Clinical (2021), Vol. 32 (34911196) (2 citations)

A novel approach to understanding Parkinsonian cognitive decline using minimum spanning trees, edge cutting, and magnetoencephalography (2021)

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ABSTRACT Graph theory-based approaches are efficient tools for detecting clustering and group-wise differences in high-dimensional data across a wide range of fields, such as gene expression analysis and neural connectivity. Here, we examine data from a cross-sectional, resting-state magnetoencephalography study of 89 Parkinson's disease patients, and use minimum-spanning tree (MST) methods to relate severity of Parkinsonian cognitive impairment to neural connectivity changes. In particular, we implement the two-sample multivariate-runs test of Friedman and Rafsky (Ann Stat 7(4):697-717, 1979) and find it to be a powerful paradigm for distinguishing highly significant deviations from the null distribution in high-dimensional data. We also generalize this test for use with greater than two classes, and show its ability to localize significance to particular sub-classes. We observe multiple indications of altered connectivity in Parkinsonian dementia that may be of future use in diagnosis and prediction.

Scientific reports (2021), Vol. 11, No. 1 (34611218) (0 citations)

Evaluation of movement and brain activity (2021)

Hallett, Mark; DelRosso, Lourdes M; Elble, Rodger; Ferri, Raffaele; Horak, Fay B; Lehericy, Stephan; Mancini, Martina; Matsuhashi, Masao; Matsumoto, Riki; Muthuraman, Muthuraman; Raethjen, Jan; Shibasaki, Hiroshi

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ABSTRACT Clinical neurophysiology studies can contribute important information about the physiology of human movement and the pathophysiology and diagnosis of different movement disorders. Some techniques can be accomplished in a routine clinical neurophysiology laboratory and others require some special equipment. This review, initiating a series of articles on this topic, focuses on the methods and techniques. The methods reviewed include EMG, EEG, MEG, evoked potentials, coherence, accelerometry, posturography (balance), gait, and sleep studies. Functional MRI (fMRI) is also reviewed as a physiological method that can be used independently or together with other methods. A few applications to patients with movement disorders

are discussed as examples, but the detailed applications will be the subject of other articles.

Keywords: Accelerometer, Coherence, EEG, EMG, Gait, Kinematics, MEG, Movement, Movement disorders, Posture, Sleep, fMRI

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2021), Vol. 132, No. 10 (34488012) (7 citations)

Neural signatures of hyperdirect pathway activity in Parkinson's disease (2021)

Oswal, Ashwini; Cao, Chunyan; Yeh, Chien-Hung; Neumann, Wolf-Julian; Gratwicke, James; Akram, Harith; Horn, Andreas; Li, Dianyou; Zhan, Shikun; Zhang, Chao; Wang, Qiang; Zrinzo, Ludvic; Foltynie, Tom; Limousin, Patricia; Bogacz, Rafal; Sun, Bomin; Husain, Masud; Brown, Peter; Litvak, Vladimir

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ABSTRACT Parkinson's disease (PD) is characterised by the emergence of beta frequency oscillatory synchronisation across the cortico-basal-ganglia circuit. The relationship between the anatomy of this circuit and oscillatory synchronisation within it remains unclear. We address this by combining recordings from human subthalamic nucleus (STN) and internal globus pallidus (GPi) with magnetoencephalography, tractography and computational modelling. Coherence between supplementary motor area and STN within the high (21-30 Hz) but not low (13-21 Hz) beta frequency range correlated with 'hyperdirect pathway' fibre densities between these structures. Furthermore, supplementary motor area activity drove STN activity selectively at high beta frequencies suggesting that high beta frequencies propagate from the cortex to the basal ganglia via the hyperdirect pathway. Computational modelling revealed that exaggerated high beta hyperdirect pathway activity can provoke the generation of widespread pathological synchrony at lower beta frequencies. These findings suggest a spectral signature and a pathophysiological role for the hyperdirect pathway in PD.

Nature communications (2021), Vol. 12, No. 1 (34465771) (18 citations)

Functional connectivity of spoken language processing in early-stage Parkinson's disease: An MEG study (2021)

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ABSTRACT Parkinson's disease (PD) is a neurodegenerative disorder, well-known for its motor symptoms; however, it also adversely affects cognitive functions, including language, a highly important human ability. PD pathology is associated, even in the early stage of the disease, with alterations in the functional connectivity within cortico-subcortical circuitry of the basal ganglia as well as within cortical networks. Here, we investigated functional cortical connectivity related to spoken language processing in early-stage PD patients. We employed a patient-friendly passive attention-free paradigm to probe neurophysiological correlates of language processing in PD patients without confounds related to active attention and overt motor responses. MEG data were recorded from a group of newly diagnosed PD patients and age-matched healthy controls who were passively presented with spoken word stimuli (action and abstract verbs, as well as grammatically correct and incorrect inflectional forms) while focussing on watching a silent movie. For each of the examined linguistic aspects, a logistic regression classifier was used to classify participants as either PD patients or healthy controls based on functional connectivity within the temporo-fronto-parietal cortical language networks. Classification was successful for action verbs (accuracy = 0.781, p-value = 0.003) and, with lower accuracy, for abstract verbs (accuracy = 0.688, p-value = 0.041) and incorrectly inflected forms (accuracy = 0.648, p-value = 0.021), but not for correctly inflected forms (accuracy = 0.523, p-value = 0.384). Our findings point to quantifiable differences in functional connectivity within the cortical systems underpinning language processing in newly diagnosed PD patients compared to healthy controls, which arise early, in the absence of clinical evidence of deficits in cognitive or general language functions. The techniques presented here may aid future work on establishing neurolinguistic markers to objectively and noninvasively identify functional changes in the brain's language networks even before clinical symptoms emerge.

Keywords: Action verb, Classification, Functional connectivity, Magnetoencephalography (MEG), Morphosyntax, Parkinson’s disease (PD)

NeuroImage. Clinical (2021), Vol. 32 (34455187) (4 citations)

Randomized controlled trial of neurologic music therapy in Parkinson's disease: research rehabilitation protocols for mechanistic and clinical investigations (2021)

Buard, Isabelle; Lattanzio, Lucas; Stewart, Rebekah; Thompson, Sarah; Sjoberg, Kristin; Hookstadt, Karen; Morrow, Meghan; Holden, Samantha K; Sillau, Stefan; Thaut, Michael; Kluger, Benzi

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BACKGROUND Presently available medications and surgical treatments for Parkinson's disease have limited effects on fine motor problems and often leave patients with significant fine motor disability. Standard of care occupational therapy (OT) yields low efficacy, potentially due to a lack of standard protocols. Neurologic music therapy (NMT) techniques, especially rhythmic auditory stimulation which relies on interaction between rhythm and movement, have shown to be effective in PD gait rehabilitation possibly through their reliance on neural pathways that are not affected by PD. Therapeutic instrumental music performance (TIMP) is one other NMT technique that holds promise but which mode of action and efficacy has not been investigated in PD yet.

METHODS One hundred PD participants will be randomly assigned to receive 15 sessions of either TIMP with rhythm or TIMP without rhythm, standard of care OT, or to be waitlisted (control) over 5 consecutive weeks. Brain oscillatory responses will be collected

using magnetoencephalography during an auditory-motor task to understand the underlying mechanisms. The Grooved Pegboard, the UPDRS III finger tap, and the finger-thumb opposition will be assessed to investigate clinical changes related to fine motor function. This project will also serve to confirm or refute our pilot data findings suggesting NMT relies on compensatory brain networks utilized by the PD brain to bypass the dysfunctional basal ganglia.

DISCUSSION This study aims to use standardized TIMP and OT research protocols for investigating the neuronal pathways utilized by each intervention and possibly study their efficacy with respect to fine motor rehabilitation via a randomized control trial in the PD population.

TRIAL REGISTRATION ClinicalTrials.gov NCT03049033 . Registered on September 29, 2020.

Keywords: Magnetoencephalography, Motor cortical activity, Neurologic music therapy, Neuronal entrainment, Parkinson's disease, Rehabilitation

Trials (2021), Vol. 22, No. 1 (34454592) (1 citation)

Brain Networks and Cognitive Impairment in Parkinson's Disease (2022)

Rucco, Rosaria; Lardone, Anna; Liparoti, Marianna; Lopez, Emahnuel Troisi; De Micco, Rosa; Tessitore, Alessandro; Granata, Carmine; Mandolesi, Laura; Sorrentino, Giuseppe; Sorrentino, Pierpaolo

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ABSTRACT Aim: The aim of the present study is to investigate the relationship between both functional connectivity and brain networks with cognitive decline, in patients with Parkinson's disease (PD). Introduction: PD phenotype is not limited to motor impairment but, rather, a wide range of non-motor disturbances can occur, with cognitive impairment being one of the most common. However, how the large-scale organization of brain activity differs in cognitively impaired patients, as opposed to cognitively preserved ones, remains poorly understood. Methods: Starting from source-reconstructed resting-state magnetoencephalography data, we applied the phase linearity measurement (PLM) to estimate functional connectivity, globally and between brain areas, in PD patients with and without cognitive impairment (respectively PD-CI and PD-NC), as compared with healthy subjects (HS). Further, using graph analysis, we characterized the alterations in brain network topology and related these, as well as the functional connectivity, to cognitive performance. Results: We found reduced global and nodal PLM in several temporal (fusiform gyrus, Heschl's gyrus, and inferior temporal gyrus), parietal (postcentral gyrus), and occipital (lingual gyrus) areas within the left hemisphere, in the gamma band, in PD-CI patients, as compared with PD-NC and HS. With regard to the global topological features, PD-CI patients, as compared with HS and PD-NC patients, showed differences in multi-frequencies bands (delta, alpha, gamma) in the Leaf fraction, Tree hierarchy (Th) (both higher in PD-CI), and Diameter (lower in PD-CI). Finally, we found statistically significant correlations between the Montreal Cognitive Assessment test and both the Diameter in delta band and the Th in the alpha band. Conclusion: Our work points to specific large-scale rearrangements that occur selectively in cognitively compromised PD patients and are correlated to cognitive impairment. Impact statement In this article, we want to test the hypothesis that the cognitive decline observed in Parkinson's disease (PD) patients may be related to specific changes of both functional connectivity and brain network topology. Specifically, starting from magnetoencephalography signals and by applying the phase linearity measurement (PLM), a connectivity metric that measures the synchronization between brain regions, we were able to highlight differences in the global and nodal PLM

values in PD patients with cognitive impairment as compared with both cognitively unimpaired patients and healthy subjects. Further, using graph analysis, we analyzed alterations in brain network topology that were related to cognitive functioning.

Keywords: brain networks topology, cognition, functional connectivity, graph theory, magnetoencephalography, synchrony

Brain connectivity (2022), Vol. 12, No. 5 (34269602) (4 citations)

Differential dopaminergic modulation of spontaneous cortico-subthalamic activity in Parkinson's disease (2021)

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ABSTRACT Pathological oscillations including elevated beta activity in the subthalamic nucleus (STN) and between STN and cortical areas are a hallmark of neural activity in Parkinson's disease (PD). Oscillations also play an important role in normal physiological processes and serve distinct functional roles at different points in time. We characterised the effect of dopaminergic medication on oscillatory whole-brain networks in PD in a time-resolved manner by employing a hidden Markov model on combined STN local field potentials and magnetoencephalography (MEG) recordings from 17 PD patients. Dopaminergic medication led to coherence within the medial and orbitofrontal cortex in the delta/theta frequency range. This is in line with known side effects of dopamine treatment such as deteriorated executive functions in PD. In addition, dopamine caused the beta band activity to switch from an STN-mediated motor network to a frontoparietal-mediated one. In contrast, dopamine did not modify local STN-STN coherence in PD. STN-STN synchrony emerged both on and off medication. By providing electrophysiological evidence for the differential effects of dopaminergic medication on the discovered networks, our findings open further avenues for electrical and pharmacological interventions in PD.

Keywords: human, local field potential, magnetoencephalography, neuroscience, time-resolved analysis, whole-brain

eLife (2021), Vol. 10 (34085932) (4 citations)

STN-DBS affects language processing differentially in Parkinson's disease: Multiple-case MEG study (2021)

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OBJECTIVES In this study, we investigated the effects of bilateral and unilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) in PD patients on neural responses associated with two aspects of spoken language processing: semantics of action-related verbs and morphosyntactic processing.

MATERIALS AND METHODS Using a passive unattended paradigm to present spoken linguistic stimuli, we recorded magnetoencephalographic (MEG) re-

sponses in three PD patients in four DBS conditions: left unilateral STN-DBS, right unilateral STN-DBS, bilateral STN-DBS, and no STN-DBS. To ensure that any observed effects of DBS on the neuromagnetic responses could be attributed to the linguistic context per se and were not merely induced by the electrical stimulation, we assessed the effects of STN-DBS on linguistic contrasts within each stimulation condition. Hence, we contrasted the processing of action vs. abstract verbs as well as the processing of correct vs. incorrect morphosyntactic inflections within each DBS condition.

RESULTS The results revealed that, compared to the DBS-off state, both bilateral and right unilateral stimulation of the STN yielded significant dissociations in the processing of action and abstract verbs, with greater neuromagnetic responses for action verbs compared to abstract verbs. For morphosyntax processing, only left unilateral stimulation yielded significant dissociations (relative to the DBS-off state), with greater neuromagnetic responses to the incorrect inflections compared to the correct inflections.

CONCLUSION The results reflect differential effects of unilateral and bilateral STN-DBS on neuromagnetic responses associated with the processing of spoken language. They suggest that different specific aspects of linguistic information processing in PD are affected differently by STN-DBS.

Keywords: Parkinson's disease, action verb, bilateral, deep brain stimulation, language, magnetoencephalography, morphosyntax, unilateral

Acta neurologica Scandinavica (2021), Vol. 144, No. 2 (33961289) (2 citations)

GABAergic cortical network physiology in frontotemporal lobar degeneration (2021)

Adams, Natalie E; Hughes, Laura E; Rouse, Matthew A; Phillips, Holly N; Shaw, Alexander D; Murley, Alexander G; Cope, Thomas E; Bevan-Jones, W Richard; Passamonti, Luca; Street, Duncan; Holland, Negin; Nesbitt, David; Friston, Karl; Rowe, James B

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ABSTRACT The clinical syndromes caused by frontotemporal lobar degeneration are heterogeneous, including the behavioural variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy. Although pathologically distinct, they share many behavioural, cognitive and physiological features, which may in part arise from common deficits of major neurotransmitters such as γ-aminobutyric acid (GABA). Here, we quantify the GABAergic impairment and its restoration with dynamic causal modelling of a double-blind placebo-controlled crossover pharmaco-magnetoencephalography study. We analysed 17 patients with bvFTD, 15 patients with progressive supranuclear palsy, and 20 healthy age- and gender-matched controls. In addition to neuropsychological assessment and structural MRI, participants undertook two magnetoencephalography sessions using a roving auditory oddball paradigm: once on placebo and once on 10 mg of the oral GABA reuptake inhibitor tiagabine. A subgroup underwent ultrahigh-field magnetic resonance spectroscopy measurement of GABA concentration, which was reduced among patients. We identified deficits in frontotemporal processing using conductance-based biophysical models of local and global neuronal networks. The clinical relevance of this physiological deficit is indicated by the correlation between top-down connectivity from frontal to temporal cortex and clinical measures of cognitive and behavioural change. A critical validation of the biophysical modelling approach was evidence from parametric empirical Bayes analysis that GABA levels in patients, measured by spectroscopy, were related to posterior estimates of patients' GABAergic synaptic connectivity. Further evidence for the role of GABA in frontotemporal lobar degeneration came from confirmation that the effects of tiagabine on local circuits depended not only on participant group, but also on individual baseline GABA levels. Specifically, the phasic inhibition of deep cortico-cortical pyramidal neurons following tiagabine, but not placebo, was a function of GABA concentration. The study provides proof-of-concept for the potential of dynamic causal modelling to elucidate mechanisms of human neurodegenerative disease, and explains the variation in response to candidate therapies among patients. The laminar- and neurotransmitter-specific features of the modelling framework, can be used to study other treatment approaches and disorders. In the context of frontotemporal lobar degeneration, we suggest that neurophysiological restoration in selected patients, by targeting neurotransmitter deficits, could be used to bridge between clinical and preclinical models of disease, and inform the personalized selection of drugs and stratification of patients for future clinical trials.

Keywords: GABA, conductance-based modelling, dynamic causal modelling, frontotemporal dementia, progressive supranuclear palsy

Brain: a journal of neurology (2021), Vol. 144, No. 7 (33710299) (10 citations)

Flexible brain dynamics underpins complex behaviours as observed in Parkinson's disease (2021)

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ABSTRACT Rapid reconfigurations of brain activity support efficient neuronal communication and flexible behaviour. Suboptimal brain dynamics is associated to impaired adaptability, possibly leading to functional deficiencies. We hypothesize that impaired flexibility in brain activity can lead to motor and cognitive symptoms of Parkinson's disease (PD). To test this hypothesis, we studied the 'functional repertoire'-the number of distinct configurations of neural activity-using source-reconstructed magnetoencephalography in PD patients and controls. We found stereotyped brain dynamics and reduced flexibility in PD. The intensity of this reduction was proportional to symptoms severity, which can be explained by beta-band hyper-synchronization. Moreover, the basal ganglia were prominently involved in the abnormal patterns of brain activity. Our findings support the hypotheses that: symptoms in PD relate to impaired brain flexibility, this impairment preferentially involves the basal ganglia, and beta-band hypersynchronization is associated with reduced brain flexibility. These findings highlight the importance of extensive functional repertoires for correct behaviour.

Scientific reports (2021), Vol. 11, No. 1 (33602980) (18 citations)

Cortical connectivity of the nucleus basalis of Meynert in Parkinson's disease and Lewy body dementias (2021)

Oswal, Ashwini; Gratwicke, James; Akram, Harith; Jahanshahi, Marjan; Zaborszky, Laszlo; Brown, Peter; Hariz, Marwan; Zrinzo, Ludvic; Foltynie, Tom; Litvak, Vladimir

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ABSTRACT Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are related conditions that are associated with cholinergic system dysfunction. Dysfunction of the nucleus basalis of Meynert (NBM), a basal forebrain structure that provides the dominant source of cortical cholinergic innervation, has been implicated in the pathogenesis of both PDD and DLB. Here we leverage the temporal resolution of magnetoencephalography with the spatial resolution of MRI tractography to explore the intersection of functional and structural connectivity of the NBM in a unique cohort of PDD and DLB patients undergoing deep brain stimulation of this structure. We observe that NBM-cortical structural and functional connectivity correlate within spatially and spectrally segregated networks including: (i) a beta band network to supplementary motor area, where activity in this region was found to drive activity in the NBM; (ii) a delta/theta band network to medial temporal lobe structures encompassing the parahippocampal gyrus; and (iii) a delta/theta band network to visual areas including lingual gyrus. These findings reveal functional networks of the NBM that are likely to subserve important roles in motor control, memory and visual function, respectively. Furthermore, they motivate future studies aimed at disentangling network contribution to disease phenotype.

Keywords: DBS, DTI, MEG, coherence, oscillations

Brain: a journal of neurology (2021), Vol. 144, No. 3 (33521808) (14 citations)

Variance in the pathophysiological impact of the hemizygosity of gamma-aminobutyric acid type A receptor subunit genes between Prader-Willi syndrome and Angelman syndrome (2021)

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INTRODUCTION Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are neurodevelopmental disorders caused by loss of function of maternally expressed UBE3A and paternally expressed contiguous genes on chromosome 15q11-13, respectively. A majority of these syndromes suffer from a large deletion of the relevant chromosome (AS Del or PWS Del), which includes biallelically expressed gamma-aminobutyric acid type A receptor subunit (GABAaR) genes, while remaining individuals present without the deletion (AS non-Del or PWS non-Del). We previously reported that AS Del, but not AS non-Del individuals, show aberrantly desynchronized somatosensory-evoked magnetic fields (SEFs) and speculated that it might reflect GABAergic dysfunction due to the hemizygosity of GABAaR genes. To verify its pathophysiological impact on PWS and AS, we analyzed the SEFs of PWS individuals.

METHOD SEFs were recorded from eight PWS Del and two PWS non-Del individuals. The latency and strength of the first peak (N1m) were compared with those of AS Del/non-Del individuals and controls, most of which were obtained earlier.

RESULTS In contrast to AS, both PWS Del and PWS non-Del showed normal SEF waveforms. Desynchronized response with delayed N1m peak latency was exclusively indicated in AS Del. N1m strength was statisti-

cally higher in AS Del and AS non-Del, but not in PWS Del and PWS non-Del.

CONCLUSIONS Our results indicate that the pathophysiological impact of the hemizygosity of GABAaR genes is lower in PWS than AS. UBE3A deficiency and the hemizygosity of GABAaR genes could synergistically deteriorate neuronal function, resulting in aberrant SEFs in AS Del.

Keywords: Angelman syndrome, GABA receptors, Prader-Willi syndrome, Somatosensory-evoked magnetic fields

Brain & development (2021), Vol. 43, No. 4 (33419637) (1 citation)

Structural and functional correlates of subthalamic deep brain stimulation-induced apathy in Parkinson's disease (2021)

Boon, Lennard I; Potters, Wouter V; Zoon, Thomas J C; van den Heuvel, Odile A; Prent, Naomi; de Bie, Rob M A; Bot, Maarten; Schuurman, P Richard; van den Munckhof, Pepijn; Geurtsen, Gert J; Hillebrand, Arjan; Stam, Cornelis J; van Rootselaar, Anne-Fleur; Berendse, Henk W

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BACKGROUND Notwithstanding the large improvement in motor function in Parkinson's disease (PD) patients treated with deep brain stimulation (DBS), apathy may increase. Postoperative apathy cannot always be related to a dose reduction of dopaminergic medication and stimulation itself may play a role.

OBJECTIVE We studied whether apathy in DBS-treated PD patients could be a stimulation effect.

METHODS In 26 PD patients we acquired apathy scores before and >6 months after DBS of the subthalamic nucleus (STN). Magnetoencephalography recordings (ON and OFF stimulation) were performed ≥6 months after DBS placement. Change in apathy severity was correlated with (i) improvement in motor function and dose reduction of dopaminergic medication, (ii) stimulation location (merged MRI and CT-scans) and (iii) stimulation-related changes in functional connectivity of brain regions that have an alleged role in apathy.

RESULTS Average apathy severity significantly increased after DBS ($p < 0.001$) and the number of patients considered apathetic increased from two to nine. Change in apathy severity did not correlate with improvement in motor function or dose reduction of dopaminergic medication. For the left hemisphere, increase in apathy was associated with a more dorsolateral stimulation location ($p = 0.010$). The increase in apathy severity correlated with a decrease in alpha1 functional connectivity of the dorsolateral prefrontal cortex ($p = 0.006$), but not with changes of the medial orbitofrontal or the anterior cingulate cortex.

CONCLUSIONS The present observations suggest that apathy after STN-DBS is not necessarily related to dose reductions of dopaminergic medication, but may be an effect of the stimulation itself. This highlights the importance of determining optimal DBS settings based on both motor and non-motor symptoms.

Keywords: Apathy, Deep brain stimulation, Functional connectivity, Magnetoencephalography, Parkinson's disease

Brain stimulation (2021), Vol. 14, No. 1 (33385593) (5 citations)

EEG and MEG primers for tracking DBS network effects (2021)

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ABSTRACT Deep brain stimulation (DBS) is an effective treatment method for a range of neurological and psychiatric disorders. It involves implantation of stimulating electrodes in a precisely guided fashion into subcortical structures and, at a later stage, chronic stimulation of these structures with an implantable pulse generator. While the DBS surgery makes it possible to both record brain activity and stimulate parts of the brain that are difficult to reach with non-invasive techniques, electroencephalography (EEG) and magnetoencephalography (MEG) provide complementary information from other brain areas, which can be used to characterize brain networks targeted through DBS. This requires, however, the careful consideration of different types of artifacts in the data acquisition and the subsequent analyses. Here, we review both the technical issues associated with EEG/MEG recordings in DBS patients and the experimental findings to date. One major line of research is simultaneous recording of local field potentials (LFPs) from DBS targets and EEG/MEG. These studies revealed a set of cortico-subcortical coherent networks functioning at distinguishable physiological frequencies. Specific network responses were linked to clinical state, task or stimulation parameters. Another experimental approach is mapping of DBS-targeted networks in chronically implanted patients by recording EEG/MEG responses during stimulation. One can track responses evoked by single stimulation pulses or bursts as well as brain state shifts caused by DBS. These studies have the potential to provide biomarkers for network responses that can be adapted to guide stereotactic implantation or optimization of stimulation parameters. This is especially important for diseases where the clinical effect of DBS is delayed or develops slowly over time. The same biomarkers could also potentially be utilized for the online control of DBS network effects in the new generation of closed-loop stimulators that are currently entering clinical use. Through future studies, the use of network biomarkers may facilitate the integration of circuit physiology into clinical decision making.

NeuroImage (2021), Vol. 224 (33059051) (12 citations)

Clinical factors affecting evoked magnetic fields in patients with Parkinson's disease (2020)

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ABSTRACT Studies on evoked responses in Parkinson's disease (PD) may be useful for elucidating the etiology and quantitative evaluation of PD. However, in previous studies, the association between evoked responses and detailed motor symptoms or cognitive functions has not been clear. This study investigated the characteristics of the visual (VEF), auditory (AEF), and somatosensory (SEF) evoked magnetic fields in patients with Parkinson's disease (PD), and the correlations between evoked fields and the patient's clinical characteristics, motor symptoms, and cognitive functions. Twenty patients with PD and 10 healthy controls (HCs) were recruited as participants. We recorded VEF, AEF, and SEF, collected clinical characteristics, performed physical examinations, and administered 10 cognitive tests. We investigated differences in the latencies of the evoked fields between patients with PD and HCs. We also evaluated the correlation of the latencies with motor symptoms and cognitive functioning. There were significant differences between the two groups in 6 of the cognitive tests, all of which suggested mild cognitive impairment in patients with PD. The latencies of the VEF N75m, P100m, N145m, AEF P50m, P100m, and SEF P60m components were greater in the patients with PD than in the HCs. The latencies mainly correlated with medication and motor symptoms, less so with cognitive tests, with some elements of the correlations remaining significant after Bonferroni correction. In conclusion, the latencies of the VEF, AEF, and SEF were greater in PD patients than in HCs and were mainly correlated with medication and motor symptoms rather than cognitive functioning. Findings from this study suggest that evoked fields may reflect basal ganglia functioning and are candidates for assessing motor symptoms or the therapeutic effects of medication in patients with PD.

PloS one (2020), Vol. 15, No. 9 (32941428) (1 citation)

Identification of nonlinear features in cortical and subcortical signals of Parkinson's Disease patients via a novel efficient measure (2020)

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ABSTRACT This study offers a novel and efficient measure based on a higher order version of autocorrelative signal memory that can identify nonlinearities in a single time series. The suggested method was applied to simultaneously recorded subthalamic nucleus (STN) local field potentials (LFP) and magnetoencephalography (MEG) from fourteen Parkinson's Disease (PD) patients who underwent surgery for deep brain stimulation. Recordings were obtained during rest for both OFF and ON dopaminergic medication states. We analyzed the bilateral LFP channels that had the maximum beta power in the OFF state and the cortical sources that had the maximum coherence with the selected LFP channels in the alpha band. Our findings revealed the inherent nonlinearity in the PD data as subcortical high beta (20-30 Hz) band and cortical alpha (8-12 Hz) band activities. While the former was discernible without medication (p=0.015), the latter was induced upon the dopaminergic medication (p<6.10[-4]). The degree of subthalamic nonlinearity was correlated with contralateral tremor severity (r=0.45, p=0.02). Conversely, for the cortical signals nonlinearity was present for the ON medication state with a peak in the alpha band and correlated with contralateral akinesia and rigidity (r=0.46, p=0.02). This correlation appeared to be independent from that of alpha power and the two measures combined explained 34 % of the variance in

contralateral akinesia scores. Our findings suggest that particular frequency bands and brain regions display nonlinear features closely associated with distinct motor symptoms and functions.

Keywords: Deep brain stimulation, Dopamine, Levodopa, Local field potentials, Neural oscillations, Nonlinearity

NeuroImage (2020), Vol. 223 (32916287) (4 citations)

Resting state activity and connectivity of the nucleus basalis of Meynert and globus pallidus in Lewy body dementia and Parkinson's disease dementia (2020)

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ABSTRACT Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are two related diseases which can be difficult to distinguish. There is no objective biomarker which can reliably differentiate between them. The synergistic combination of electrophysiological and neuroimaging approaches is a powerful method for interrogation of functional brain networks in vivo. We recorded bilateral local field potentials (LFPs) from the nucleus basalis of Meynert (NBM) and the internal globus pallidus (GPi) with simultaneous cortical magnetoencephalography (MEG) in six PDD and five DLB patients undergoing surgery for deep brain stimulation (DBS) to look for differences in underlying resting-state network pathophysiology. In both patient groups we observed spectral peaks in the theta (2-8 Hz) band in both the NBM and the GPi. Furthermore, both the NBM and the GPi exhibited similar spatial and spectral patterns of coupling with the cortex in the two disease states. Specifically, we report two distinct coherent networks between the NBM/GPi and cortical regions: (1) a theta band (2-8 Hz) network linking the NBM/GPi to temporal cortical regions, and (2) a beta band (13-22 Hz) network coupling the NBM/GPi to sensorimotor areas. We also found differences between the two disease groups: oscillatory power in the low beta (13-22Hz) band was significantly higher in the globus pallidus in PDD patients compared to DLB, and coherence in the high beta (22-35Hz) band between the globus pallidus and lateral sensorimotor cortex was significantly higher in DLB patients compared to PDD. Overall, our findings reveal coherent networks of the NBM/GPi region that are common to both DLB and PDD. Although the neurophysiological differences between the two conditions in this study are confounded by systematic differences in DBS lead trajectories and motor symptom severity, they lend support to the hypothesis that DLB and PDD, though closely related, are distinguishable from a neurophysiological perspective.

Keywords: Basal forebrain, Basal ganglia, Human, Network, Pallidum

NeuroImage (2020), Vol. 221 (32711059) (10 citations)

L-dopa treatment increases oscillatory power in the motor cortex of Parkinson's disease patients (2020)

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ABSTRACT Parkinson's disease (PD) is a movement disorder caused by dopaminergic neurodegeneration. Levodopa (L-dopa) is an effective medication for alleviating motor symptoms in PD that has been shown previously to reduce subcortical beta (13-30 Hz) oscillations. How L-dopa influences oscillations in the motor cortex is unclear. In this study, 21 PD patients were recorded with magnetoencephalography (MEG) in L-dopa ON and OFF states. Oscillatory components of resting-state power spectra were compared between the two states and the significant effect was localized using beamforming. Unified Parkinson's Disease Rating Scale (UPDRS) III akinesia and rigidity sub-scores for the most affected hemibody were correlated with source power values for the contralateral hemisphere. An L-dopa-induced power increase was found over the central sensors significant in the 18-30 Hz range (F(1,20) > 14.8, PFWE corr < 0.05, cluster size inference with P = 0.001 cluster-forming threshold). Beamforming localization of this effect revealed distinct peaks at the bilateral sensorimotor cortex. A significant correlation between the magnitude of L-dopa induced 18-30 Hz oscillatory motor-cortical power increase and the degree of improvement in contralateral akinesia and rigidity was found (F(2, 19) = 4.9, pone-tailed = 0.02, R[2] = 0.2). Power in the same range was also inversely correlated with combined akinesia and rigidity scores in the L-dopa OFF state (F(2, 19) = 9.2, ptwo-tailed = 0.007, R[2] = 0.33) but not in the L-dopa ON state (F(2, 19) = 0.27, ptwo-tailed = 0.6, R[2] = 0.01). These results suggest that the role of motor cortical beta oscillations in PD is distinct from that of subcortical beta.

Keywords: Cortex, Dopamine, Human, M1, Movement disorders

NeuroImage. Clinical (2020), Vol. 26 (32361482) (10 citations)

Motor effects of deep brain stimulation correlate with increased functional connectivity in Parkinson's disease: An MEG study (2020)

Boon, Lennard I; Hillebrand, Arjan; Potters, Wouter V; de Bie, Rob M A; Prent, Naomi; Bot, Maarten; Schuurman, P Richard; Stam, Cornelis J; van Rootselaar, Anne-Fleur; Berendse, Henk W

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ABSTRACT Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established symptomatic treatment in Parkinson's disease, yet its mechanism of action is not fully understood. Locally in the STN, stimulation lowers beta band power, in parallel with symptom relief. Therefore, beta band oscillations are sometimes referred to as "anti-kinetic". However, in recent studies functional interactions have been observed beyond the STN, which we hypothesized to reflect clinical effects of DBS. Resting-state, whole-brain magnetoencephalography (MEG) recordings and assessments on motor function were obtained in 18 Parkinson's disease patients with bilateral STN-DBS, on and off stimulation. For each brain region, we estimated source-space spectral power and functional connectivity with the rest of the brain. Stimulation led to an increase in average peak frequency and a suppression of absolute band power (delta to low-beta band) in the sensorimotor cortices. Significant changes (decreases and increases) in low-beta band functional connectivity were observed upon stimulation. Improvement in bradykinesia/rigidity was significantly related to increases in alpha2 and low-beta band functional connectivity (of sensorimotor regions, the cortex as a whole, and

subcortical regions). By contrast, tremor improvement did not correlate with changes in functional connectivity. Our results highlight the distributed effects of DBS on the resting-state brain and suggest that DBS-related improvements in rigidity and bradykinesia, but not tremor, may be mediated by an increase in alpha2 and low-beta functional connectivity. Beyond the local effects of DBS in and around the STN, functional connectivity changes in these frequency bands might therefore be considered as "pro-kinetic".

Keywords: Deep brain stimulation, Magnetoencephalography, Motor symptoms, Parkinson's disease, Resting-state

NeuroImage. Clinical (2020), Vol. 26 (32120294) (7 citations)

Dissecting beta-state changes during timed movement preparation in Parkinson's disease (2020)

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ABSTRACT An emerging perspective describes beta-band (15-28 Hz) activity as consisting of short-lived high-amplitude events that only appear sustained in conventional measures of trial-average power. This has important implications for characterising abnormalities observed in beta-band activity in disorders like Parkinson's disease. Measuring parameters associated with beta-event dynamics may yield more sensitive measures, provide more selective diagnostic neural markers, and provide greater mechanistic insight into the breakdown of brain dynamics in this disease. Here, we used magnetoencephalography in eighteen Parkinson's disease participants off dopaminergic medication and eighteen healthy control participants to investigate beta-event dynamics during timed movement preparation. We used the Hidden Markov Model to classify event dynamics in a data-driven manner and derived three parameters of beta events: (1) beta-state amplitude, (2) beta-state lifetime, and (3) beta-state interval time. Of these, changes in beta-state interval time explained the overall decreases in beta power during timed movement preparation and uniquely captured the impairment in such preparation in patients with Parkinson's disease. Thus, the increased granularity of the Hidden Markov Model analysis (compared with conventional analysis of power) provides increased sensitivity and suggests a possible reason for impairments of timed movement preparation in Parkinson's disease.

Keywords: Beta oscillations, Burst-events, Movement, Parkinson’s disease, Timing

Progress in neurobiology (2020), Vol. 184 (31778771) (14 citations)

Magnetization transfer saturation reveals subclinical optic nerve injury in pediatric-onset multiple sclerosis (2023)

Longoni, Giulia; Martinez Chavez, Edgar; Young, Kimberly; Brown, Robert A; Bells, Sonya; Fetco, Dumitru; Kim, Laura; Grover, Stephanie A; Costello, Fiona; Reginald, Arun; Bar-Or, Amit; Marrie, Ruth Ann; Arnold, Douglas L; Narayanan, Sridar; Branson, Helen M; Banwell, Brenda L; Sled, John G; Mabbott, Donald J; Yeh, E Ann

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BACKGROUND The presence of subclinical optic nerve (ON) injury in youth living with pediatric-onset MS has not been fully elucidated. Magnetization transfer saturation (MTsat) is an advanced magnetic resonance imaging (MRI) parameter sensitive to myelin density and microstructural integrity, which can be applied to the study of the ON.

OBJECTIVE The objective of this study was to investigate the presence of subclinical ON abnormalities in pediatric-onset MS by means of magnetization transfer saturation and evaluate their association with other structural and functional parameters of visual pathway integrity.

METHODS Eleven youth living with pediatric-onset MS (ylPOMS) and no previous history of optic neuritis and 18 controls underwent standardized brain MRI, optical coherence tomography (OCT), Magnetoencephalography (MEG)-Visual Evoked Potentials (VEPs), and visual battery. Data were analyzed with mixed effect models.

RESULTS While ON volume, OCT parameters, occipital MEG-VEPs outcomes, and visual function did not differ significantly between ylPOMS and controls, ylPOMS had lower MTsat in the supratentorial normal appearing white matter (-0.26 nU, $p = 0.0023$), and in both in the ON (-0.62 nU, $p < 0.001$) and in the normal appearing white matter of the optic radiation (-0.56 nU, $p = 0.00071$), with these being positively correlated (+0.57 nU, $p = 0.00037$).

CONCLUSIONS Subclinical microstructural injury affects the ON of ylPOMS. This may appear as MTsat changes before being detectable by other currently available testing.

Keywords: Pediatric MS, magnetization transfer, optic nerve, optical coherence tomography, quantitative MRI, visual functions

Multiple sclerosis (Houndmills, Basingstoke, England) (2023), Vol. 29, No. 2 (36545918) (0 citations)

Multistage classification identifies altered cortical phase- and amplitude-coupling in Multiple Sclerosis (2022)

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ABSTRACT Distinguishing groups of subjects or experimental conditions in a high-dimensional feature space is a common goal in modern neuroimaging studies. Successful classification depends on the selection of relevant features as not every neuronal signal component or parameter is informative about the research question at hand. Here, we developed a novel unsupervised multistage analysis approach that combines dimensionality reduction, bootstrap aggregating and multivariate classification to select relevant neuronal features. We tested the approach by identifying changes of brain-wide electrophysiological coupling in Multiple Sclerosis. Multiple Sclerosis is a demyelinating disease of the central nervous system that can result in cognitive decline and physical disability. However, related changes in large-scale brain interactions remain poorly understood and corresponding non-invasive biomarkers are sparse. We thus compared brain-wide phase- and amplitude-coupling of frequency specific neuronal activity in relapsing-remitting Multiple Sclerosis patients (n = 17) and healthy controls (n = 17) using magnetoencephalography. Changes in this dataset included both, increased and decreased phase- and amplitude-coupling in wide-spread, bilateral neuronal networks across a broad range of frequencies. These changes allowed to successfully classify patients and controls with an accuracy of 84%. Furthermore, classification confidence predicted behavioral scores of disease severity. In sum, our results unravel systematic changes of large-scale phase- and amplitude coupling in Multiple Sclerosis. Furthermore, our results establish a new analysis approach to efficiently contrast high-dimensional neuroimaging data between experimental groups or conditions.

Keywords: Amplitude-coupling, Functional connectivity, Human connectome project, MEG, Multiple Sclerosis, Multivariate classification, Neuronal oscillations, Phase-coupling

NeuroImage (2022), Vol. 264 (36400377) (0 citations)

Topological reorganization of brain network might contribute to the resilience of cognitive functioning in mildly disabled relapsing remitting multiple sclerosis (2023)

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ABSTRACT Multiple sclerosis (MS) is an inflammatory and demyelinating disease which leads to impairment in several functional systems including cognition. Alteration of brain networks is linked to disability and its

progression. However, results are mostly cross-sectional and yet contradictory as putative adaptive and maladaptive mechanisms were found. Here, we aimed to explore longitudinal reorganization of brain networks over 2-years by combining diffusion tensor imaging (DTI), resting-state functional MRI (fMRI), magnetoencephalography (MEG), and a comprehensive neuropsychological-battery. In 37 relapsing-remitting MS (RRMS) and 39 healthy-controls, cognition remained stable over-time. We reconstructed network models based on the three modalities and analyzed connectivity in relation to the hierarchical topology and functional subnetworks. Network models were compared across modalities and in their association with cognition using linear-mixed-effect-regression models. Loss of hub connectivity and global reduction was observed on a structural level over-years ($p < .010$), which was similar for functional MEG-networks but not for fMRI-networks. Structural hub connectivity increased in controls ($p = .044$), suggesting a physiological mechanism of healthy aging. Despite a general loss in structural connectivity in RRMS, hub connectivity was preserved ($p = .002$) over-time in default-mode-network (DMN). MEG-networks were similar to DTI and weakly correlated with fMRI in MS ($p < .050$). Lower structural (β between .23-.33) and both lower (β between .40-.59) and higher functional connectivity ($\beta = -.54$) in DMN was associated with poorer performance in attention and memory in RRMS ($p < .001$). MEG-networks involved no association with cognition. Here, cognitive stability despite ongoing neurodegeneration might indicate a resilience mechanism of DMN hubs mimicking a physiological reorganization observed in healthy aging.

Keywords: aging, cognition, connectivity, maladaption/adaption, relapsing remitting multiple sclerosis

Journal of neuroscience research (2023), Vol. 101, No. 1 (36263462) (0 citations)

Whole-Brain Propagation Delays in Multiple Sclerosis, a Combined Tractography-Magnetoencephalography Study (2022)

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ABSTRACT Two structurally connected brain regions are more likely to interact, with the lengths of the structural bundles, their widths, myelination, and the topology of the structural connectome influencing the timing of the interactions. We introduce an in vivo approach for measuring functional delays across the whole brain in humans (of either sex) using magneto/electroencephalography (MEG/EEG) and integrating them with the structural bundles. The resulting topochronic map of the functional delays/velocities shows that larger bundles have faster velocities. We estimated the topochronic map in multiple sclerosis patients, who have damaged myelin sheaths, and controls, demonstrating greater delays in patients across the network and that structurally lesioned tracts were slowed down more than unaffected ones. We provide a novel framework for estimating functional transmission delays in vivo at the single-subject and single-tract level.SIGNIFICANCE STATEMENT This article provides a straightforward way to estimate patient-specific delays and conduction velocities in the CNS, at the individual level, in healthy and diseased subjects. To do so, it uses

a principled way to merge magnetoencephalography (MEG)/electroencephalography (EEG) and tractography.

Keywords: brain criticality, brain dynamics, brain networks, conduction velocities, magnetoencephalography, multiple sclerosis

The Journal of neuroscience: the official journal of the Society for Neuroscience (2022), Vol. 42, No. 47 (36241383) (1 citation)

Impaired saccadic eye movements in multiple sclerosis are related to altered functional connectivity of the oculomotor brain network (2021)

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BACKGROUND Impaired eye movements in multiple sclerosis (MS) are common and could represent a non-invasive and accurate measure of (dys)functioning of interconnected areas within the complex brain network. The aim of this study was to test whether altered saccadic eye movements are related to changes in functional connectivity (FC) in patients with MS.

METHODS Cross-sectional eye movement (pro-saccades and anti-saccades) and magnetoencephalography (MEG) data from the Amsterdam MS cohort were included from 176 MS patients and 33 healthy controls. FC was calculated between all regions of the Brainnetome atlas in six conventional frequency bands. Cognitive function and disability were evaluated by previously validated measures. The relationships between saccadic parameters and both FC and clinical scores in MS patients were analysed using multivariate linear regression models.

RESULTS In MS pro- and anti-saccades were abnormal compared to healthy controls A relationship of saccadic eye movements was found with FC of the oculomotor network, which was stronger for regional than global FC. In general, abnormal eye movements were related to higher delta and theta FC but lower beta FC. Strongest associations were found for pro-saccadic latency and FC of the precuneus (beta band $\beta = -0.23$, $p = .006$), peak velocity and FC of the parietal eye field (theta band $\beta = -0.25$, $p = .005$) and gain and FC of the inferior frontal eye field (theta band $\beta = -0.25$, $p = .003$). Pro-saccadic latency was also strongly associated with disability scores and cognitive dysfunction.

CONCLUSIONS Impaired saccadic eye movements were related to functional connectivity of the oculomotor network and clinical performance in MS. This study also showed that, in addition to global network connectivity, studying regional changes in MEG studies could yield stronger correlations.

Keywords: Biomarkers, Brain network function, Eye movement, Magnetoencephalography, Multiple sclerosis, Neuro-ophthalmology

NeuroImage. Clinical (2021), Vol. 32 (34624635) (2 citations)

The utility of Magnetoencephalography in multiple sclerosis - A systematic review (2021)

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INTRODUCTION Magnetoencephalography (MEG), allows for a high degree temporal and spatial accuracy in recording cortical oscillatory activity and evoked fields. To date, no review has been undertaken to synthesise all MEG studies in Multiple Sclerosis (MS). We undertook a Systematic Review of the utility of MEG in MS.

METHODS We identified MEG studies carried out in MS using EMBASE, Medline, Cochrane, TRIP and Psychinfo databases. We included original research articles with a cohort of minimum of five multiple sclerosis patients and quantifying of at least one MEG parameter. We used a modified version of the JBI (mJBI) for case-control studies to assess for risk of bias.

RESULTS We identified 30 studies from 13 centres involving at least 433 MS patients and 347 controls. We found evidence that MEG shows perturbed activity (most commonly reduced power modulations), reduced connectivity and association with altered clinical function in Multiple Sclerosis. Specific replicated findings were decreased motor induced responses in the beta band, diminished increase of gamma power after visual stimulation, increased latency and reduced connectivity for somatosensory evoked fields. There was an association between upper alpha connectivity and cognitive measures in people with MS. Overall studies were of moderate quality (mean mJBI score 6.7).

DISCUSSION We find evidence for the utility of MEG in Multiple Sclerosis. Event-related designs are of particular value and show replicability between centres. At this stage, it is not clear whether these changes are specific to Multiple Sclerosis or are also observable in other diseases. Further studies should look to explore cognitive control in more depth using in-task designs and undertake longitudinal studies to determine whether these changes have prognostic value.

Keywords: Biomarker, Cognition, Connectivity, Magnetoencephalography, Multiple sclerosis, Neuroinflammation

NeuroImage. Clinical (2021), Vol. 32 (34537682) (1 citation)

Increased brain atrophy and lesion load is associated with stronger lower alpha MEG power in multiple sclerosis patients (2021)

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ABSTRACT In multiple sclerosis, the interplay of neurodegeneration, demyelination and inflammation leads to changes in neurophysiological functioning. This study aims to characterize the relation between reduced brain volumes and spectral power in multiple sclerosis patients and matched healthy subjects. During resting-state eyes closed, we collected magnetoencephalographic data in 67 multiple sclerosis patients and 47 healthy subjects, matched for age and gender. Additionally, we quantified different brain volumes through magnetic resonance imaging (MRI). First, a principal component analysis of MRI-derived brain volumes demonstrates that atrophy can be largely described by two components: one overall degenerative component that correlates strongly with different cognitive tests, and one component that mainly captures degeneration of the cortical grey matter that strongly correlates with age. A multimodal correlation analysis indicates that increased brain atrophy and lesion load is accompanied by increased spectral power in the lower alpha (8-10 Hz) in the temporoparietal junction (TPJ). Increased lower alpha power in the TPJ was further associated with worse results on verbal and spatial working memory tests, whereas an increased lower/upper alpha power ratio was associated with slower information processing speed. In conclusion, multiple sclerosis patients with increased brain atrophy, lesion and thalamic volumes demonstrated increased lower alpha power in the TPJ and reduced cognitive abilities.

Keywords: Magnetoencephalography, Multiple sclerosis, Resting state, Spectral power, Structural neuroimaging

NeuroImage. Clinical (2021), Vol. 30 (33770549) (3 citations)

Functional brain network organization measured with magnetoencephalography predicts cognitive decline in multiple sclerosis (2021)

Nauta, Ilse M; Kulik, Shanna D; Breedt, Lucas C; Eijlers, Anand Jc; Strijbis, Eva Mm; Bertens, Dirk; Tewarie, Prejaas; Hillebrand, Arjan; Stam, Cornelis J; Uitdehaag, Bernard Mj; Geurts, Jeroen Jg; Douw, Linda; de Jong, Brigit A; Schoonheim, Menno M

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BACKGROUND Cognitive decline remains difficult to predict as structural brain damage cannot fully explain the extensive heterogeneity found between MS patients.

OBJECTIVE To investigate whether functional brain network organization measured with magnetoencephalography (MEG) predicts cognitive decline in MS patients after 5 years and to explore its value beyond structural pathology.

METHODS Resting-state MEG recordings, structural MRI, and neuropsychological assessments were ana-

lyzed of 146 MS patients, and 100 patients had a 5-year follow-up neuropsychological assessment. Network properties of the minimum spanning tree (i.e. backbone of the functional brain network) indicating network integration and overload were related to baseline and longitudinal cognition, correcting for structural damage.

RESULTS A more integrated beta band network (i.e. smaller diameter) and a less integrated delta band network (i.e. lower leaf fraction) predicted cognitive decline after 5 years (Radj2=15%), independent of structural damage. Cross-sectional analyses showed that a less integrated network (e.g. lower tree hierarchy) related to worse cognition, independent of frequency band.

CONCLUSIONS The level of functional brain network integration was an independent predictive marker of cognitive decline, in addition to the severity of structural damage. This work thereby indicates the promise of MEG-derived network measures in predicting disease progression in MS.

Keywords: Multiple sclerosis, cognitive functioning, longitudinal, magnetic resonance imaging, magnetoencephalography, network organization

Multiple sclerosis (Houndmills, Basingstoke, England) (2021), Vol. 27, No. 11 (33295249) (7 citations)

The role of hippocampal theta oscillations in working memory impairment in multiple sclerosis (2021)

Costers, Lars; Van Schependom, Jeroen; Laton, Jorne; Baijot, Johan; Sjøgård, Martin; Wens, Vincent; De Tiège, Xavier; Goldman, Serge; D'Haeseleer, Miguel; D'hooghe, Marie Beatrice; Woolrich, Mark; Nagels, Guy

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ABSTRACT Working memory (WM) problems are frequently present in people with multiple sclerosis (MS). Even though hippocampal damage has been repeatedly shown to play an important role, the underlying neurophysiological mechanisms remain unclear. This study aimed to investigate the neurophysiological underpinnings of WM impairment in MS using magnetoencephalography (MEG) data from a visual-verbal 2-back task. We analysed MEG recordings of 79 MS patients and 38 healthy subjects through event-related fields and theta (4-8 Hz) and alpha (8-13 Hz) oscillatory processes. Data was source reconstructed and parcellated based on previous findings in the healthy subject sample. MS patients showed a smaller maximum theta power increase in the right hippocampus between 0 and 400 ms than healthy subjects ($p = .014$). This theta power increase value correlated negatively with reaction time on the task in MS ($r = -.32$, $p = .029$). Evidence was provided that this relationship could not be explained by a 'common cause' confounding relationship with MS-related neuronal damage. This study provides the first neurophysiological evidence of the influence of hippocampal dysfunction on WM performance in MS.

Keywords: hippocampus, magnetoencephalography, multiple sclerosis, n-back, theta, working memory

Human brain mapping (2021), Vol. 42, No. 5 (33247542) (5 citations)

Brain dysconnectivity relates to disability and cognitive impairment in multiple sclerosis (2021)

Sjøgård, Martin; Wens, Vincent; Van Schependom, Jeroen; Costers, Lars; D'hooghe, Marie; D'haeseleer, Miguel; Woolrich, Mark; Goldman, Serge; Nagels, Guy;

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ABSTRACT The pathophysiology of cognitive dysfunction in multiple sclerosis (MS) is still unclear. This magnetoencephalography (MEG) study investigates the impact of MS on brain resting-state functional connectivity (rsFC) and its relationship to disability and cognitive impairment. We investigated rsFC based on power envelope correlation within and between different frequency bands, in a large cohort of participants consisting of 99 MS patients and 47 healthy subjects. Correlations were investigated between rsFC and outcomes on disability, disease duration and 7 neuropsychological scores within each group, while stringently correcting for multiple comparisons and possible confounding factors. Specific dysconnections correlating with MS-induced physical disability and disease duration were found within the sensorimotor and language networks, respectively. Global network-level reductions in within- and cross-network rsFC were observed in the default-mode network. Healthy subjects and patients significantly differed in their scores on cognitive fatigue and verbal fluency. Healthy subjects and patients showed different correlation patterns between rsFC and cognitive fatigue or verbal fluency, both of which involved a shift in patients from the posterior default-mode network to the language network. Introducing electrophysiological rsFC in a regression model of verbal fluency and cognitive fatigue in MS patients significantly increased the explained variance compared to a regression limited to structural MRI markers (relative thalamic volume and lesion load). This MEG study demonstrates that MS induces distinct changes in the resting-state functional brain architecture that relate to disability, disease duration and specific cognitive functioning alterations. It highlights the potential value of electrophysiological intrinsic rsFC for monitoring the cognitive impairment in patients with MS.

Keywords: cognitive fatigue, cognitive impairment, functional connectivity, magnetoencephalography, multiple sclerosis

Human brain mapping (2021), Vol. 42, No. 3 (33242237)
(14 citations)

Structural correlates of atypical visual and motor cortical oscillations in pediatric-onset multiple sclerosis (2020)

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ABSTRACT We have previously demonstrated that pediatric-onset multiple sclerosis (POMS) negatively impacts the visual pathway as well as motor processing speed. Relationships between MS-related diffuse structural damage of gray and white matter (WM) tissue and cortical responses to visual and motor stimuli remain poorly understood. We used magnetoencephalography in 14 POMS patients and 15 age- and sex-matched healthy controls to assess visual gamma (30-80 Hz), motor gamma (60-90 Hz), and motor beta (15-30 Hz) cortical oscillatory responses to a visual-motor task. Then, 3T MRI was used to: (a) calculate fractional anisotropy (FA) of the posterior visual and corticospinal motor WM pathways and (b) quantify volume and thickness of the cuneus and primary motor cortex. Visual gamma band power was reduced in POMS and was associated with reduced FA of the optic radiations but not with loss of cuneus volume or thickness. Activity in the primary

motor cortex, as measured by postmovement beta rebound amplitude associated with peak latency, was decreased in POMS, although this reduction was not predicted by structural metrics. Our findings implicate loss of WM integrity as a contributor to reduced electrical responses in the visual cortex in POMS. Future work in larger cohorts will inform on the cognitive implications of this finding in terms of visual processing function and will determine whether the progressive loss of brain volume known to occur in POMS ultimately contributes to both progressive dysfunction in such tasks as well as progressive reduction in cortical electrical responses in the visual cortex.

Keywords: MEG, diffusion tensor imaging, magnetic resonance imaging, multiple sclerosis, pediatrics, postmovement beta rebound, visual gamma band

Human brain mapping (2020), Vol. 41, No. 15 (32648649) (6 citations)

Cross-network coupling of neural oscillations in the dynamic pain connectome reflects chronic neuropathic pain in multiple sclerosis (2020)

Kim, Junseok A; Bosma, Rachael L; Hemington, Kasey S; Rogachov, Anton; Osborne, Natalie R; Cheng, Joshua C; Oh, Jiwon; Dunkley, Benjamin T; Davis, Karen D

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ABSTRACT Sensory perceptions are coded by complex neural dynamics of regional communication in the brain. Thus, sensory abnormalities such as chronic pain may occur when neural dynamics go awry. Previous studies of cross-network dynamic functional connectivity in chronic pain identified abnormalities but were based on functional MRI which only captures slow temporal features. Here we conducted a magnetoencephalography (MEG) study to investigate fine temporal dynamics of aberrant cross-regional and cross-network communication of the dynamic pain connectome in patients with chronic pain. We also introduced a novel measure, dynamic functional coupling, to quantify the variability of brain communication. The study was performed in 33 people who had chronic pain associated with multiple sclerosis and 30 healthy controls. We found that patients with chronic pain exhibited abnormalities in cross-network functional coupling across multiple frequency bands (theta, alpha, beta, gamma), between the salience network and 3 other networks: the ascending nociceptive pathway, descending antinociceptive pathway, and the default mode network. However, these cross-network abnormalities involved different frequency bands in patients with neuropathic versus non-neuropathic chronic pain. Furthermore, cross-network abnormalities were linked to pain severity and pain interference. Our findings implicate broadband cross-network abnormalities as hallmark features of chronic pain in multiple sclerosis.

Keywords: Chronic pain, Dynamic functional coupling, Functional connectivity, Magnetoencephalography, Oscillations

NeuroImage. Clinical (2020), Vol. 26 (32143136) (15 citations)

Pain

Resting-state magnetoencephalographic oscillatory connectivity to identify patients with chronic migraine using machine learning (2022)

Hsiao, Fu-Jung; Chen, Wei-Ta; Pan, Li-Ling Hope; Liu, Hung-Yu; Wang, Yen-Feng; Chen, Shih-Pin; Lai, Kuan-Lin; Coppola, Gianluca; Wang, Shuu-Jiun

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ABSTRACT To identify and validate the neural signatures of resting-state oscillatory connectivity for chronic migraine (CM), we used machine learning techniques to classify patients with CM from healthy controls (HC) and patients with other pain disorders. The cross-sectional study obtained resting-state magnetoencephalographic data from 240 participants (70 HC, 100 CM, 35 episodic migraine [EM], and 35 fibromyalgia [FM]). Source-based oscillatory connectivity of relevant cortical regions was calculated to determine intrinsic connectivity at 1-40 Hz. A classification model that employed a support vector machine was developed using the magnetoencephalographic data to assess the reliability and generalizability of CM identification. In the findings, the discriminative features that differentiate CM from HC were principally observed from the functional interactions between salience, sensorimotor, and part of the default mode networks. The classification model with these features exhibited excellent performance in distinguishing patients with CM from HC (accuracy ≥ 86.8%, area under the curve (AUC) ≥ 0.9) and from those with EM (accuracy: 94.5%, AUC: 0.96). The model also achieved high performance (accuracy: 89.1%, AUC: 0.91) in classifying CM from other pain disorders (FM in this study). These resting-state magnetoencephalographic electrophysiological features yield oscillatory connectivity to identify patients with CM from those with a different type of migraine and pain disorder, with adequate reliability and generalizability.

Keywords: Chronic migraine, Machine learning, Magnetoencephalography, Pain disorders, Resting-state oscillatory connectivity

The journal of headache and pain (2022), Vol. 23, No. 1 (36192689) (0 citations)

A Hidden Markov Model reveals magnetoencephalography spectral frequency-specific abnormalities of brain state power and phase-coupling in neuropathic pain (2022)

Fauchon, Camille; Kim, Junseok A; El-Sayed, Rima; Osborne, Natalie R; Rogachov, Anton; Cheng, Joshua C; Hemington, Kasey S; Bosma, Rachael L; Dunkley, Benjamin T; Oh, Jiwon; Bhatia, Anuj; Inman, Robert D; Davis, Karen Deborah

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ABSTRACT Neuronal populations in the brain are engaged in a temporally coordinated manner at rest. Here we show that spontaneous transitions between large-scale resting-state networks are altered in chronic neuropathic pain. We applied an approach based on the Hidden Markov Model to magnetoencephalography data to describe how the brain moves from one activity state to another. This identified 12 fast transient (~80 ms) brain states including the sensorimotor, ascending nociceptive pathway, salience, visual, and default mode networks. Compared to healthy controls, we found that people with neuropathic pain exhibited abnormal alpha power in the right ascending nociceptive pathway state, but higher power and coherence in the sensorimotor network state in the beta band, and shorter time intervals between visits of the sensorimotor network, indicating more active time in this state. Conversely, the neuropathic pain group showed lower coherence and spent less time in the frontal attentional state. Therefore, this study reveals a temporal imbalance and dysregulation of spectral frequency-specific brain microstates in patients with neuropathic pain. These findings can potentially impact the development of a mechanism-based therapeutic approach by identifying brain targets to stimulate using neuromodulation to modify abnormal activity and to restore effective neuronal synchrony between brain states.

Communications biology (2022), Vol. 5, No. 1 (36131088) (0 citations)

Neurofeedback Training without Explicit Phantom Hand Movements and Hand-Like Visual Feedback to Modulate Pain: A Randomized Crossover Feasibility Trial (2022)

Yanagisawa, Takufumi; Fukuma, Ryohei; Seymour, Ben; Tanaka, Masataka; Yamashita, Okito; Hosomi, Koichi; Kishima, Haruhiko; Kamitani, Yukiyasu; Saitoh, Youichi

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ABSTRACT Phantom limb pain is attributed to abnormal sensorimotor cortical representations, although the causal relationship between phantom limb pain and sensorimotor cortical representations suffers from the potentially confounding effects of phantom hand movements. We developed neurofeedback training to change sensorimotor cortical representations without explicit phantom hand movements or hand-like visual feedback. We tested the feasibility of neurofeedback training in fourteen patients with phantom limb pain. Neurofeedback training was performed in a single-blind, randomized, crossover trial using two decoders constructed using motor cortical currents measured during phantom hand movements; the motor cortical currents contralateral or ipsilateral to the phantom hand (contralateral and ipsilateral training) were estimated from magnetoencephalograms. Patients were instructed to control the size of a disk, which was proportional to the decoding results, but to not move their phantom hands or other body parts. The pain assessed by the visual analogue scale was significantly greater after contralateral training than after ipsilateral training. Classification accuracy of phantom hand movements significantly increased only after contralat-

eral training. These results suggested that the proposed neurofeedback training changed phantom hand representation and modulated pain without explicit phantom hand movements or hand-like visual feedback, thus showing the relation between the phantom hand representations and pain. PERSPECTIVE: Our work demonstrates the feasibility of using neurofeedback training to change phantom hand representation and modulate pain perception without explicit phantom hand movements and hand-like visual feedback. The results enhance the mechanistic understanding of certain treatments, such as mirror therapy, that change the sensorimotor cortical representation.

Keywords: Phantom limb pain, brain–computer interface, magnetoencephalography, neurofeedback training, sensorimotor plasticity

The journal of pain (2022), Vol. 23, No. 12 (35932992) (0 citations)

Headache-related circuits and high frequencies evaluated by EEG, MRI, PET as potential biomarkers to differentiate chronic and episodic migraine: Evidence from a systematic review (2022)

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BACKGROUND The diagnosis of migraine is mainly clinical and self-reported, which makes additional examinations unnecessary in most cases. Migraine can be subtyped into chronic (CM) and episodic (EM). Despite the very high prevalence of migraine, there are no evidence-based guidelines for differentiating between these subtypes other than the number of days of migraine headache per month. Thus, we consider it timely to perform a systematic review to search for physiological evidence from functional activity (as opposed to anatomical structure) for the differentiation between CM and EM, as well as potential functional biomarkers. For this purpose, Web of Science (WoS), Scopus, and PubMed databases were screened.

FINDINGS Among the 24 studies included in this review, most of them (22) reported statistically significant differences between the groups of CM and EM. This finding is consistent regardless of brain activity acquisition modality, ictal stage, and recording condition for a wide variety of analyses. That speaks for a supramodal and domain-general differences between CM and EM that goes beyond a differentiation based on the days of migraine per month. Together, the reviewed studies demonstrates that electro- and magneto-physiological brain activity (M/EEG), as well as neurovascular and metabolic recordings from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), show characteristic patterns that allow to differentiate between CM and EM groups.

CONCLUSIONS Although a clear brain activity-based biomarker has not yet been identified to distinguish these subtypes of migraine, research is approaching headache specialists to a migraine diagnosis based not only on symptoms and signs reported by patients. Future studies based on M/EEG should pay special attention to the brain activity in medium and fast frequency bands, mainly the beta band. On the other hand, fMRI and PET studies should focus on neural circuits and regions related to pain and emotional processing.

Keywords: Chronic migraine (CM), Electroencephalography (EEG), Episodic migraine (EM), Functional activity, Functional magnetic resonance imaging (fMRI), Magnetoencephalography (MEG), Positron emission tomography (PET)

The journal of headache and pain (2022), Vol. 23, No. 1 (35927625) (1 citation)

Racial outgroup favoritism in neural responses to others' pain emerges during sociocultural interactions (2022)

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ABSTRACT Racial ingroup favoritism in empathic brain activity has been widely observed and is associated with biased behavior toward same-race and other-race individuals. We investigated whether racial outgroup favoritism in neural responses to others' pain - an objective measure of empathy - may emerge during sociocultural interactions in a new social environment. We recorded magnetoencephalography to pain and neutral expressions of Asian and White faces from White students who had stayed in China for 6-36 weeks (Experimental group) or 2-4 weeks (Control group). The experimental group showed better neural decoding of and greater insular/sensorimotor responses to pain vs. neutral expressions of Asian compared to White faces. By contrast, the control group showed better neural decoding of pain vs. neutral expressions of White than Asian faces. In addition, participants of the experimental group who had stayed longer in China showed greater sensorimotor responses to pain (vs. neutral) expressions of Asian faces but weaker sensorimotor responses to pain (vs. neutral) expressions of White faces. Our findings revealed emerging racial outgroup favoritism in brain activities associated with sensorimotor resonance and affective sharing of others' pain during sociocultural interactions.

Keywords: Empathy, Insula, MEG, Pain expression, Racial outgroup favoritism

Neuropsychologia (2022), Vol. 174 (35835232) (0 citations)

A Review of Effects of Spinal Cord Stimulation on Spectral Features in Resting-State Electroencephalography (2023)

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BACKGROUND Spinal cord stimulation (SCS) is an effective therapy for patients with refractory chronic pain syndromes. Although studies have shown that SCS has both spinal and supraspinal effects, the current understanding of cortical effects is still limited. Neuroimaging techniques, such as magnetoencephalography (MEG) and electroencephalography (EEG), combined here as M/EEG, can reveal modulations in ongoing resting-state cortical activity. We aim to provide an overview of available literature on resting-state M/EEG in patients with chronic pain who have been treated with SCS.

MATERIALS AND METHODS We searched multiple online data bases for studies on SCS, chronic pain, and resting-state M/EEG. Primary outcome measures were changes in spectral features, combined with brain regions in which these changes occurred.

RESULTS We included eight studies reporting various SCS paradigms (tonic, burst, high-dose, and high-frequency stimulation) and revealing heterogeneity in outcome parameters. We summarized changes in cortical activity in various frequency bands: theta (4-7 Hz), alpha (7-12 Hz), beta (13-30 Hz), and gamma (30-44 Hz). In multiple studies, the somatosensory cortex showed modulation of cortical activity under tonic, burst, and high-frequency stimulation. Changes in connectivity were found in the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and parahippocampus.

CONCLUSIONS The large heterogeneity observed in outcome measures is probably caused by the large variety in study designs, stimulation paradigms, and spectral features studied. Paresthesia-free paradigms have been compared with tonic stimulation in multiple studies. These studies suggest modulation of medial, lateral, and descending pathways for paresthesia-free stimulation, whereas tonic stimulation predominantly modulates lateral and descending pathways. Moreover, multiple studies have reported an increased alpha peak frequency, increased alpha power, and/or decreased theta power when SCS was compared with baseline, indicating modulation of thalamocortical pathways. Further studies with well-defined groups of responders and nonresponders to SCS are recommended to independently study the cortical effects of pain relief and SCS.

Keywords: Chronic pain, Spinal cord stimulation (SCS), cortical activity, electroencephalography (EEG), magnetoencephalography (MEG)

Neuromodulation: journal of the International Neuromodulation Society (2023), Vol. 26, No. 1 (35551867) (0 citations)

Unveiling the phantom: What neuroimaging has taught us about phantom limb pain (2022)

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ABSTRACT Phantom limb pain (PLP) is a complicated condition with diverse clinical challenges. It consists of pain perception of a previously amputated limb. The exact pain mechanism is disputed and includes mechanisms involving cerebral, peripheral, and spinal origins. Such controversy limits researchers' and clinicians' ability to develop consistent therapeutics or management. Neuroimaging is an essential tool that can address this problem. This review explores diffusion tensor imaging, functional magnetic resonance imaging, electroencephalography, and magnetoencephalography in the context of PLP. These imaging modalities have distinct mechanisms, implications, applications, and limitations. Diffusion tensor imaging can outline structural changes and has surgical applications. Functional magnetic resonance imaging captures functional changes with spatial resolution and has therapeutic applications. Electroencephalography and magnetoencephalography can identify functional changes with a strong temporal resolution. Each imaging technique provides a unique perspective and they can be used in concert to reveal the true nature of PLP. Furthermore, researchers can utilize the respective strengths of each neuroimaging technique to support the development of innovative therapies. PLP exemplifies how neuroimaging and clinical management are intricately connected. This review can assist clinicians and researchers seeking a foundation for applications and understanding the limitations of neuroimaging techniques in the context of PLP.

Keywords: DTI, EEG, MEG, fMRI, phantom limb pain

Brain and behavior (2022), Vol. 12, No. 3 (35218308) (1 citation)

Complexity Assessment of Chronic Pain in Elderly Knee Osteoarthritis Based on Neuroimaging Recognition Techniques (2021)

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ABSTRACT The chronic pain of knee osteoarthritis in the elderly is investigated in detail in this paper, as well as the complexity of chronic pain utilising neuroimaging recognition techniques. Chronic pain in knee osteoarthritis (KOA) has a major effect on patients' quality of life and functional activities; therefore, understanding the causes of KOA pain and the analgesic advantages of different therapies is important. In recent years, neuroimaging techniques have become increasingly important in basic and clinical pain research. Thanks to the application and development of neuroimaging techniques in the study of chronic pain in KOA, researchers have found that chronic pain in KOA contains both injury-receptive and neuropathic pain components. The neuropathic pain mechanism that causes KOA pain is complicated, and it may be produced by peripheral or central sensitization, but it has not gotten enough attention in clinical practice, and there is no agreement on how to treat combination neuropathic pain KOA. As a result, using neuroimaging techniques such as magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), and near-infrared spectroscopy (NIRS), this review examines the changes in brain pathophysiology-related regions caused by KOA pain, compares the latest results in pain assessment and prediction, and clarifies the central brain analgesic mechanistic. The capsule network model is introduced in this paper from the perspective of deep learning network structure to construct an information-complete and reversible image low-level feature bridge using isotropic representation, predict the corresponding capsule features from MRI voxel responses, and then, complete the accurate reconstruction of simple images using inverse transformation. The proposed model improves the structural similarity index by about 10%, improves the reconstruction performance of low-level feature content in simple images by about 10%, and achieves feature interpretation and analysis of low-level visual cortical fMRI voxels by visualising capsule features, according to the experimental results.

Computational and mathematical methods in medicine (2021), Vol. 2021 (34876922) (1 citation)

Exploring sex differences in alpha brain activity as a potential neuromarker associated with neuropathic pain (2022)

Fauchon, Camille; Kim, Junseok A; El-Sayed, Rima; Osborne, Natalie R; Rogachov, Anton; Cheng, Joshua C; Hemington, Kasey S; Bosma, Rachael L; Dunkley, Benjamin T; Oh, Jiwon; Bhatia, Anuj; Inman, Robert D; Davis, Karen D

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ABSTRACT Alpha oscillatory activity (8-13 Hz) is the dominant rhythm in the awake brain and is known to play an important role in pain states. Previous studies have identified alpha band slowing and increased power in the dynamic pain connectome (DPC) of people with chronic neuropathic pain. However, a link between alpha-band abnormalities and sex differences in brain organization in healthy individuals and those with chronic pain is not known. Here, we used resting-state magnetoencephalography to test the hypothesis that peak alpha frequency (PAF) abnormalities are general features across chronic central and peripheral conditions causing neuropathic pain but exhibit sex-specific differences in networks of the DPC (ascending nociceptive pathway [ANP], default mode network, salience network [SN], and subgenual anterior cingulate cortex). We found that neuropathic pain (N = 25 men and 25 women) was associated with increased PAF power in the DPC compared with 50 age- and sex-matched healthy controls, whereas slower PAF in nodes of the SN (temporoparietal junction) and the ANP (posterior insula) was associated with higher trait pain intensity. In the neuropathic pain group, women exhibited lower PAF power in the subgenual anterior cingulate cortex and faster PAF in the ANP and SN than men. The within-sex analyses indicated that women had neuropathic pain-related increased PAF power in the ANP, SN, and default mode network, whereas men with neuropathic pain had increased PAF power restricted to the ANP. These findings highlight neuropathic pain-related and sex-specific abnormalities in alpha oscillations across

the DPC that could underlie aberrant neuronal communication in nociceptive processing and modulation.

Pain (2022), Vol. 163, No. 7 (34711764) (4 citations)

Paired Acute Invasive/Non-invasive Stimulation (PAINS) study: A phase I/II randomized, sham-controlled crossover trial in chronic neuropathic pain (2021)

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BACKGROUND Dorsal root ganglion (DRG) stimulation, an invasive method of neuromodulation, and transcranial direct current stimulation (tDCS), a non-invasive method of altering cortical excitability, have both proven effective in relieving chronic pain.

OBJECTIVE We employed a randomized, sham-controlled crossover study design to investigate whether single-session tDCS would have an additive therapeutic effect alongside DRG stimulation (DRGS) in the treatment of chronic pain.

METHODS Sixteen neuropathic pain patients who were previously implanted with DRG stimulators were recruited. Baseline pain scores were established with DRGS-OFF. Pain scores were then recorded with DRGS-ON, after paired sham tDCS stimulation, and after paired active anodal tDCS (a-tDCS) stimulation. For active tDCS, patients were randomized to 'MEG (magnetoencephalography) localized' tDCS or contralateral motor cortex (M1) tDCS for 30 min. EEG recordings and evaluations of tDCS adverse effects were also collected.

RESULTS All participants reported the interventions to be tolerable with no significant adverse effects during the session. Paired DRGS/active tDCS resulted in a significant reduction in pain scores compared to paired DRGS-ON/sham tDCS or DRGS alone. There was no difference in the additive effect of M1 vs. MEG-localized tDCS. Significant augmentation of beta activity was observed between DRGS-OFF and DRGS-ON conditions, as well as between paired DRGS-ON/sham tDCS and paired DRGS-ON/active tDCS.

CONCLUSION Our results indicate that a single session of tDCS alongside DRGS is safe and can significantly reduce pain acutely in neuropathic pain patients. Paired invasive/non-invasive neuromodulation is a promising new treatment strategy for pain management and should be evaluated further to assess long-term benefits.

Keywords: Chronic pain, Dorsal root ganglion stimulation, EEG, Transcranial direct current stimulation

Brain stimulation (2021), Vol. 14, No. 6 (34673258) (2 citations)

Migraine chronification is associated with beta-band connectivity within the pain-related cortical regions: a magnetoencephalographic study (2021)

Hsiao, Fu-Jung; Chen, Wei-Ta; Liu, Hung-Yu; Wang, Yen-Feng; Chen, Shih-Pin; Lai, Kuan-Lin; Hope Pan, Li-Ling; Coppola, Gianluca; Wang, Shuu-Jiun

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ABSTRACT Pain disorders are associated with aberrant oscillations in the pain-related cortical regions; however, few studies have investigated the relationship between the functional cortical network and migraine chronification through direct neural signals. Magnetoencephalography was used to record the resting-state

brain activity of healthy controls as well as patients with episodic migraine (EM) and chronic migraine (CM). The source-based oscillatory dynamics of the pain-related cortical regions, which comprises 10 node regions (the bilateral primary [SI] and secondary somatosensory cortices, insula, medial frontal cortex, and anterior cingulate cortex [ACC]), were calculated to determine the intrinsic connectivity and node strength at 1 to 40 Hz. The total node strength within the pain-related cortical regions was smaller in the beta band in patients with migraine (70 EM and 80 CM) than in controls (n = 65). In the beta band, the node strength and functional connectivity values of patients with CM and patients with EM differed from those of controls in specific cortical areas, notably the left SI (EM < control) and bilateral ACC (CM < control); moreover, the node strength was lower in patients with CM than in those with EM. In all patients with migraine, negative correlations were observed between headache frequency and node strength in the bilateral ACC. In conclusion, migraine is characterized by reduced beta oscillatory connectivity within the pain-related cortical regions. Reduced beta connectivity in the ACC is linked to migraine chronification. Longitudinal studies should verify whether this oscillation change is a brain signature and a potential neuromodulation target for migraine.

Pain (2021), Vol. 162, No. 10 (34534180) (6 citations)

Supraspinal Effects of Dorsal Root Ganglion Stimulation in Chronic Pain Patients (2021)

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OBJECTIVES Dorsal root ganglion stimulation (DRGS) has become a popular neuromodulatory treatment for neuropathic pain. We used magnetoencephalography (MEG) to investigate potential biomarkers of pain and pain relief, based on the differences in power spectral density (PSD) during varying degrees of pain and how these oscillations change during DRGS-mediated pain relief.

MATERIALS AND METHODS Thirteen chronic pain patients with implanted dorsal root ganglion stimulators were included in the MEG analysis. MEG Recordings were performed at rest while the stimulator was turned ON or OFF. Numerical rating scale (NRS) scores were also recorded before and after DRGS was turned OFF and ON. Power spectral and source localization analyses were then performed on preprocessed MEG recordings.

RESULTS With DRGS-OFF, patients in severe pain had significantly increased cortical theta (4-7 Hz) power and decreased cortical alpha (7-13 Hz) power compared to patients reporting less pain. This shift in power toward lower frequencies was contrasted by a shift toward the higher frequency power spectrum (low beta 13-20 Hz activity) during DRGS-mediated pain relief. A significant correlation was found between the increase in low beta activity and the degree of reported pain relief.

CONCLUSION Our results demonstrate increased low-frequency power spectral activity in chronic pain patients in the absence of stimulation which shifts toward higher frequency power spectrum activity in response to therapeutic DRGS. These cortical changes in response to DRGS provide support for the use of neuroimaging in the search for potential biomarkers of pain.

Keywords: Case series, DRG stimulation, MEG, chronic pain, complex regional pain syndrome, failed back surgery syndrome, neuropathic pain, neurostimulation, peripheral nerve stimulation, postherpetic neuralgia

Neuromodulation: journal of the International Neuromodulation Society (2021), Vol. 24, No. 4 (33974317) (2 citations)

How expectations of pain elicited by consciously and unconsciously perceived cues unfold over time (2021)

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ABSTRACT Expectation can shape the perception of pain within a fraction of time, but little is known about how perceived expectation unfolds over time and modulates pain perception. Here, we combine magnetoencephalography (MEG) and machine learning approaches to track the neural dynamics of expectations of pain in healthy participants with both sexes. We found that the expectation of pain, as conditioned by facial cues, can be decoded from MEG as early as 150 ms and up to 1100 ms after cue onset, but decoding expectation elicited by unconsciously perceived cues requires more time and decays faster compared to consciously perceived ones. Also, results from temporal generalization suggest that neural dynamics of decoding cue-based expectation were predominately sustained during cue presentation but transient after cue presentation. Finally, although decoding expectation elicited by consciously perceived cues were based on a series of time-restricted brain regions during cue presentation, decoding relied on the medial prefrontal cortex and anterior cingulate cortex after cue presentation for both consciously and unconsciously perceived cues. These findings reveal the conscious and unconscious processing of expectation during pain anticipation and may shed light on enhancing clinical care by demonstrating the impact of expectation cues.

Keywords: Conditioning, Conscious and unconscious, Expectation of pain, Machine learning, Neural dynamics, Temporal decoding, Temporal generalization

NeuroImage (2021), Vol. 235 (33762214) (2 citations)

A novel beamformer-based imaging of phase-amplitude coupling (BIPAC) unveiling the inter-regional connectivity of emotional prosody processing in women with primary dysmenorrhea (2021)

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ABSTRACT Objective. Neural communication or the interactions of brain regions play a key role in the formation of functional neural networks. A type of neural communication can be measured in the form of phase-amplitude coupling (PAC), which is the coupling between the phase of low-frequency oscillations and the amplitude of high-frequency oscillations. This paper presents a beamformer-based imaging method, beamformer-based imaging of PAC (BIPAC), to quantify the strength of PAC between a seed region and other brain regions.Approach. A dipole is used to model the ensemble of neural activity within a group of nearby neurons and represents a mixture of multiple source components of cortical activity. From ensemble activity at each brain location, the source component with the strongest coupling to the seed activity is extracted, while unrelated components are suppressed to enhance the sensitivity of coupled-source estimation.Main results. In evaluations using simulation

data sets, BIPAC proved advantageous with regard to estimation accuracy in source localization, orientation, and coupling strength. BIPAC was also applied to the analysis of magnetoencephalographic signals recorded from women with primary dysmenorrhea in an implicit emotional prosody experiment. In response to negative emotional prosody, auditory areas revealed strong PAC with the ventral auditory stream and occipitoparietal areas in the theta-gamma and alpha-gamma bands, which may respectively indicate the recruitment of auditory sensory memory and attention reorientation. Moreover, patients with more severe pain experience appeared to have stronger coupling between auditory areas and temporoparietal regions.Significance. Our findings indicate that the implicit processing of emotional prosody is altered by menstrual pain experience. The proposed BIPAC is feasible and applicable to imaging inter-regional connectivity based on cross-frequency coupling estimates. The experimental results also demonstrate that BIPAC is capable of revealing autonomous brain processing and neurodynamics, which are more subtle than active and attended task-driven processing.

Keywords: beamformer, cross-frequency coupling (CFC), emotional prosody, magnetoencephalography (MEG), neural communication, phase-amplitude coupling (PAC), primary dysmenorrhea (PDM)

Journal of neural engineering (2021), Vol. 18, No. 4 (33691295) (1 citation)

Individual pain sensitivity is associated with resting-state cortical activities in healthy individuals but not in patients with migraine: a magnetoencephalography study (2020)

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BACKGROUND Pain sensitivity may determine the risk, severity, prognosis, and efficacy of treatment of clinical pain. Magnetic resonance imaging studies have linked thermal pain sensitivity to changes in brain structure. However, the neural correlates of mechanical pain sensitivity remain to be clarified through investigation of direct neural activities on the resting-state cortical oscillation and synchrony.

METHODS We recorded the resting-state magnetoencephalographic (MEG) activities of 27 healthy individuals and 30 patients with episodic migraine (EM) and analyzed the source-based oscillatory powers and functional connectivity at 2 to 59 Hz in pain-related cortical regions, which are the bilateral anterior cingulate cortex (ACC), medial orbitofrontal (MOF) cortex, lateral orbitofrontal (LOF) cortex, insula cortex, primary somatosensory cortex (SI), primary motor cortex (MI), and posterior cingulate cortex (PCC). The mechanical punctate pain threshold (MPPT) was obtained at the supraorbital area (the first branch of the trigeminal nerve dermatome, V1) and the forearm (the first thoracic nerve dermatome, T1) and further correlated with MEG measures.

RESULTS The MPPT is inversely correlated with the resting-state relative powers of gamma oscillation in healthy individuals (all corrected $P < 0.05$). Specifically, inverse correlation was noted between the MPPT at V1 and gamma powers in the bilateral insula ($r = -0.592$ [left] and -0.529 [right]), PCC ($r = -0.619$ and -0.541) and MI ($r = -0.497$ and -0.549) and between the MPPT at T1 and powers in the left PCC ($r = -0.561$) and bilateral MI ($r = -0.509$ and -0.520). Furthermore, resting-state functional connectivity at the delta to beta bands, especially between frontal (MOF, ACC, LOF, and MI), parietal (PCC), and sensorimotor (bilateral SI and MI) regions, showed a positive correlation with the MPPT at V1 and T1 (all corrected $P < 0.05$). By contrast, in patients with EM, the MPPT was not associated with resting-state cortical activities.

CONCLUSIONS Pain sensitivity in healthy individuals is associated with the resting-state gamma oscillation and functional connectivity in pain-related cortical regions. Further studies must be conducted in a large population to confirm whether resting-state cortical activities can be an objective measurement of pain sensitivity in individuals without clinical pain.

Keywords: Episodic migraine, Functional connectivity, Gamma, Magnetoencephalography, Oscillation, Pain sensitivity, Resting state

The journal of headache and pain (2020), Vol. 21, No. 1 (33198621) (5 citations)

Sex-differences in network level brain dynamics associated with pain sensitivity and pain interference (2021)

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ABSTRACT Neural dynamics can shape human experience, including pain. Pain has been linked to dynamic functional connectivity within and across brain regions of the dynamic pain connectome (consisting of the ascending nociceptive pathway (Asc), descending antinociceptive pathway (Desc), salience network (SN), and the default mode network (DMN)), and also shows sex differences. These linkages are based on fMRI-derived slow hemodynamics. Here, we utilized the fine temporal resolution of magnetoencephalography (MEG) to measure resting state functional coupling (FCp) related to individual pain perception and pain interference in 50 healthy individuals (26 women, 24 men). We found that pain sensitivity and pain interference were linked to within- and cross-network broadband FCp across the Asc and SN. We also identified sex differences in these relationships: (a) women exhibited greater within-network static FCp, whereas men had greater dynamic FCp within the dynamic pain connectome; (b) relationship between pain sensitivity and pain interference with FCp in women was commonly found in theta, whereas in men, these relationships were predominantly in the beta and low gamma bands. These findings indicate that dynamic interactions of brain networks underlying pain involve fast brain communication in men but slower communication in women.

Keywords: functional connectivity, magnetoencephalography, network dynamics, pain, sex differences

Human brain mapping (2021), Vol. 42, No. 3 (33068500) (5 citations)

Neural Oscillations: Understanding a Neural Code of Pain (2021)

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ABSTRACT Neural oscillations play an important role in the integration and segregation of brain regions that are important for brain functions, including pain. Disturbances in oscillatory activity are associated with several disease states, including chronic pain. Studies of neural oscillations related to pain have identified several functional bands, especially alpha, beta, and gamma bands, implicated in nociceptive processing. In this review, we introduce several properties of neural oscillations that are important to understand the role of brain oscillations in nociceptive processing. We also discuss the role of neural oscillations in the maintenance of efficient communication in the brain. Finally, we discuss the role of neural oscillations in healthy and chronic pain nociceptive processing. These data and concepts illustrate the key role of regional and inter-

regional neural oscillations in nociceptive processing underlying acute and chronic pains.

Keywords: chronic pain, connectivity, magnetoencephalography (MEG), oscillations, pain

The Neuroscientist: a review journal bringing neurobiology, neurology and psychiatry (2021), Vol. 27, No. 5 (32981457) (22 citations)

Neural dynamics of pain expression processing: Alpha-band synchronization to same-race pain but desynchronization to other-race pain (2021)

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ABSTRACT Both electroencephalography and functional magnetic resonance imaging studies have revealed enhanced neural responses to perceived pain in same-race than other-race individuals. However, it remains unclear how neural responses in the sensorimotor, cognitive, and affective subsystems vary dynamically in the first few hundreds of milliseconds to generate racial ingroup favoritism in empathy for pain. We recorded magnetoencephalography signals to pain and neutral expressions of Asian and white faces from Chinese adults during judgments of racial identity of each face. We found that pain compared to neutral expressions of same-race faces induced early increased alpha oscillations in the precuneus/parietal cortices followed by increased alpha-band oscillations in the left anterior insula and temporoparietal junction. Pain compared to neutral expressions of other-race faces, however, induced early suppression of alpha-band oscillations in the bilateral sensorimotor cortices and left insular cortex. Moreover, decreased functional connectivity between the left sensorimotor cortex and left anterior insula predicted reduced subjective feelings of other-race suffering. Our results unraveled distinct patterns of modulations of neural dynamics of sensorimotor, affective, and cognitive components of empathy by interracial relationships between an observer and a target person, which provide possible brain mechanisms for understanding racial ingroup favoritism in social behavior.

Keywords: Alpha oscillation, Empathy, MEG, Race, Pain expression

NeuroImage (2021), Vol. 224 (32979524) (9 citations)

BCI training to move a virtual hand reduces phantom limb pain: A randomized crossover trial (2020)

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OBJECTIVE To determine whether training with a brain-computer interface (BCI) to control an image of a phantom hand, which moves based on cortical currents estimated from magnetoencephalographic signals, reduces phantom limb pain.

METHODS Twelve patients with chronic phantom limb pain of the upper limb due to amputation or brachial plexus root avulsion participated in a randomized single-blinded crossover trial. Patients were trained to move the virtual hand image controlled by the BCI with a real decoder, which was constructed to classify intact hand movements from motor cortical currents, by moving their phantom hands for 3 days ("real training"). Pain was evaluated using a visual analogue scale (VAS) before and after training, and at follow-up for an additional 16 days. As a control, patients engaged in the training with the same hand image controlled by randomly changing values ("random training"). The 2 trainings were randomly assigned to the patients. This trial is registered at UMIN-CTR (UMIN000013608).

RESULTS VAS at day 4 was significantly reduced from the baseline after real training (mean [SD], 45.3 [24.2]-30.9 [20.6], 1/100 mm; $p = 0.009 < 0.025$), but not after random training ($p = 0.047 > 0.025$). Compared to VAS at day 1, VAS at days 4 and 8 was significantly reduced by 32% and 36%, respectively, after real training and was significantly lower than VAS after random training ($p < 0.01$).

CONCLUSION Three-day training to move the hand images controlled by BCI significantly reduced pain for 1 week.

CLASSIFICATION OF EVIDENCE This study provides Class III evidence that BCI reduces phantom limb pain.

Neurology (2020), Vol. 95, No. 4 (32675074) (5 citations)

Disturbance of somatotopic spatial cognition and extra-territorial pain in carpal tunnel syndrome (2020)

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BACKGROUND Several studies on carpal tunnel syndrome have reported pain that exists beyond the median nerve territory of the affected hand. However, the mechanism is unknown.

PURPOSE We investigated the cause of extra-territorial pain by the analysis of clinical assessments and cortical activity using magnetoencephalography.

METHODS To compare patients with and without extra-territorial pain, fourteen patients with carpal tunnel syndrome were assessed using clinical examination, such as patients' profile, paresthesia, physical tests, and psychological tests. The physical assessment included tactile threshold and static and moving two-point discrimination sensations on digital pulp. Neural activation in the cerebral cortex was also measured using z-scores calculated by magnetoencephalography.

RESULTS Among fourteen patients, ten patients had pain in the affected median nerve territory only and four patients had extra-territorial pain. When comparing the groups, the static and moving two-point discrimination sensation values in patients with extra-territorial pain were larger than those of patients without the pain ($p<0.05$). The supra-marginal gyrus, mid-part of the precentral sulcus, angular gyrus in the left hemisphere, bilateral sensorimotor areas for legs, and bilateral isthmus-cingulate areas showed larger z-scores in patients with extra-territorial pain than in patients without the pain ($p<0.05$).

CONCLUSIONS The static and moving two-point discrimination sensations signify the ability of tactile spatial acuity. Bilateral sensorimotor areas were activated in sites that were not the hand. Furthermore, the inferior parietal lobule in the left hemisphere, which synthesizes and integrates multiple sensations showed high activation. Our findings suggested that the mechanism of extra-territorial pain was associated with dysfunction of spatial cognition.

Keywords: Pain, carpal tunnel syndrome, inferior parietal lobule, magnetoencephalography, spatial cognition

NeuroRehabilitation (2020), Vol. 46, No. 3 (32250335) (1 citation)

Abnormal alpha band power in the dynamic pain connectome is a marker of chronic pain with a neuropathic component (2020)

Kisler, Lee B; Kim, Junseok A; Hemington, Kasey S; Rogachov, Anton; Cheng, Joshua C; Bosma, Rachael L; Osborne, Natalie R; Dunkley, Benjamin T; Inman, Robert D; Davis, Karen D

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ABSTRACT We previously identified alpha frequency slowing and beta attenuation in the dynamic pain connectome related to pain severity and interference in patients with multiple sclerosis-related neuropathic pain (NP). Here, we determined whether these abnormalities, are markers of aberrant temporal dynamics in non-neuropathic inflammatory pain (non-NP) or when NP is also suspected. We measured resting-state magnetoencephalography (MEG) spectral density in 45 people (17 females, 28 males) with chronic back pain due to ankylosing spondylitis (AS) and 38 age/sex matched healthy controls. We used painDETECT scores to divide the chronic pain group into those with only non-NP (NNP) and those who likely also had a component of NP in addition to their inflammatory pain. We also assessed pain severity, pain interference, and disease activity with the Brief Pain Inventory and Bath AS Disease Activity Index (BASDAI). We examined spectral power in the dynamic pain connectome, including nodes of the ascending nociceptive pathway (ANP), default mode (DMN), and salience networks (SN). Compared to the healthy controls, the AS patients exhibited increased theta power in the DMN and decreased low-gamma power in the DMN and ANP, but did not exhibit beta-band attenuation or peak-alpha slowing. The NNP patients were not different from HCs. Compared to both healthy controls and NNP, NP patients had increased alpha power in the ANP. Increased alpha power within the ANP was associated with reduced BASDAI in the NNP group, and increased pain in the mixed-NP group within the DMN, SN, and ANP. Thus, high theta and low gamma activity may be markers of chronic pain but high alpha-band activity may relate to particular features of neuropathic chronic pain.

Keywords: Chronic pain, Default mode network, Magnetoencephalography, Neuropathic pain, Salience network, Somatosensory cortex

NeuroImage. Clinical (2020), Vol. 26 (32203904) (20 citations)

Cross-network coupling of neural oscillations in the dynamic pain connectome reflects chronic neuropathic pain in multiple sclerosis (2020)

Kim, Junseok A; Bosma, Rachael L; Hemington, Kasey S; Rogachov, Anton; Osborne, Natalie R; Cheng, Joshua C; Oh, Jiwon; Dunkley, Benjamin T; Davis, Karen D

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ABSTRACT Sensory perceptions are coded by complex neural dynamics of regional communication in the brain. Thus, sensory abnormalities such as chronic pain may occur when neural dynamics go awry. Previous studies of cross-network dynamic functional connectivity in chronic pain identified abnormalities but were based on functional MRI which only captures slow temporal features. Here we conducted a magnetoencephalography (MEG) study to investigate fine temporal dynamics of aberrant cross-regional and cross-network communication of the dynamic pain connectome in patients with chronic pain. We also introduced a novel measure, dynamic functional coupling, to quantify the variability of brain communication. The study was performed in 33 people who had chronic pain associated with multiple sclerosis and 30 healthy controls. We found that patients with chronic pain exhibited abnormalities in cross-network functional coupling across multiple frequency bands (theta, alpha, beta, gamma), between the salience network and 3 other networks: the ascending nociceptive pathway, descending antinociceptive pathway, and the default mode network. However, these cross-network abnormalities involved different frequency bands in patients with neuropathic versus non-neuropathic chronic pain. Furthermore, cross-network abnormalities were linked to pain severity and pain interference. Our findings implicate broadband cross-network abnormalities as hallmark features of chronic pain in multiple sclerosis.

Keywords: Chronic pain, Dynamic functional coupling, Functional connectivity, Magnetoencephalography, Oscillations

NeuroImage. Clinical (2020), Vol. 26 (32143136) (15 citations)

Noninvasive muscle activity imaging using magnetography (2020)

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ABSTRACT A spectroscopic paradigm has been developed that allows the magnetic field emissions generated by the electrical activity in the human body to be imaged in real time. The growing significance of imaging modalities in biology is evident by the almost exponential increase of their use in research, from the molecular to the ecological level. The method of analysis described here allows totally noninvasive imaging of muscular activity (heart, somatic musculature). Such imaging can be obtained without additional methodological steps such as the use of contrast media.

Keywords: magnetocardiography, magnetoencephalography, magnetomyograph, precise frequency-pattern analysis

Proceedings of the National Academy of Sciences of the United States of America (2020), Vol. 117, No. 9 (32071237) (5 citations)

Acute Exercise Modulates Pain-induced Response on Sensorimotor Cortex 20 Hz Oscillation (2020)

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ABSTRACT Exercise affects positively on self-reported pain in musculoskeletal pain conditions possibly via top-down pain inhibitory networks. However, the role of cortical activity in these networks is unclear. The aim of the current exploratory study was to investigate the effects of acute exercise on cortical nociceptive processing and specifically the excitability in the human sensorimotor cortex. Five healthy adults (mean age 32.8 years) were recorded with a whole-head 306-channel magnetoencephalography (MEG, Elekta Neuromag® Triux™). Participant's right hand third fingertip was stimulated electrically with an intracutaneous non-magnetic copper tip electrode before and immediately after an exercise task. Stimulus intensity was set individually so that the stimulation was subjectively rated as moderately painful, 6-7 on a visual analog scale. The acute exercise task was an isometric three-minute fatiguing left hand contraction with force-level at 30% of maximum voluntary contraction. Data analysis was conducted as event-related evoked field and frequency analysis. Early cortical activations after stimulation were localized in the primary and secondary somatosensory cortices. The main result demonstrated modulation of cortical nociceptive processing in the sensorimotor cortex 20 Hz rhythm immediately after the acute exercise. In conclusion, acute exercise may have an effect on nociceptive processing in the sensorimotor cortex on oscillatory level. Research on cortical oscillations analyzing interaction between nociception and exercise is limited. This study presents results indicating brain oscillatory activity as a feasible research target for examining mechanisms interacting between exercise and cortical nociceptive processing.

Keywords: brain oscillations, electrical stimulation, exercise, magnetoencephalography, sensorimotor cortex

Neuroscience (2020), Vol. 429 (31935493) (4 citations)

Bilateral activations in operculo-insular area show temporal dissociation after peripheral electrical stimulation in healthy adults (2020)

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ABSTRACT Interhemispheric transfer is necessary for sensory integration and coordination of body sides. We studied how somatosensory input from one body side may reach both body sides. First, we investigated with 17 healthy adults in which uni- and bilateral brain areas were involved in consecutive stages of automatic sensory processing of non-nociceptive peripheral stimulation. Somatosensory evoked fields (SEFs) to electrical stimulation were recorded with 306-channel magnetoencephalography in two conditions. First, SEFs were registered following sensory radial nerve (RN) stimulation to dorsal surface of the right hand and second, following median nerve (MN) stimulation at the right wrist. Cortical activations were located in contralateral postcentral gyrus after MN and RN stimulations and in bilateral operculo-insular area after RN stimulation. First component occurred earlier after MN than RN stimulation. Middle latency components had similar latencies with stronger activation in contralateral postcentral gyrus after MN than RN stimulation. Interestingly, long latency components located in bilateral operculo-insular area after RN stimulation showed latency difference between hemispheres, i.e. activation peaked earlier in contralateral than in ipsilateral side. Additional experiments comparing novel intracutaneous nociceptive, RN and MN electrical stimuli confirmed bilateral long latency activation elicited by each stimulus type and highlighted latency differences between hemispheres.

Variations in activation of bilateral operculo-insular areas may corroborate their role in pain network and in multisensory integration. Our findings imply that these areas present a relay station in multisensory stimulus detection.

Keywords: magnetoencephalography, median nerve, nociception, radial nerve, sensory cortex

The European journal of neuroscience (2020), Vol. 52, No. 12 (29766591) (2 citations)

Post-Traumatic Stress Disorder

MEG neural signature of sexual trauma in women veterans with PTSD (2022)

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ABSTRACT Previous research has documented the utility of synchronous neural interactions (SNI) in classifying women veterans with and without posttraumatic stress disorder (PTSD) and other trauma-related outcomes based on functional connectivity using magnetoencephalography (MEG). Here, we extend that line of research to evaluate trauma-specific PTSD neural signatures with MEG in women veterans. Participants completed diagnostic interviews and underwent a task-free MEG scan from which SNI was computed. Thirty-five women veterans were diagnosed with PTSD due to sexual trauma and sixteen with PTSD due to non-sexual trauma. Strength of SNI was compared in women with and without sexual trauma, and linear discriminant analysis was used to classify the brain patterns of women with PTSD due to sexual trauma and non-sexual trauma. Comparison of SNI strength between the two groups revealed widespread hypercorrelation in women with sexual trauma relative to those without sexual trauma. Furthermore, using SNI, the brains of participants were classified as sexual trauma or non-sexual trauma with 100% accuracy. These findings bolster evidence supporting the utility of task-free SNI and suggest that neural signatures of PTSD are trauma-specific.

Keywords: Biomarker, Magnetoencephalography, Post-traumatic stress disorder, Sexual trauma

Experimental brain research (2022), Vol. 240, No. 7-8 (35786746) (2 citations)

Neural oscillations while remembering traumatic memories in post-traumatic stress disorder (2022)

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OBJECTIVE The current study investigated the oscillatory brain activity of PTSD patients during directed and imaginal exposure to the traumatic memory using magnetoencephalography (MEG), in a paradigm resembling exposure therapy.

METHODS Brain activity of healthy trauma-exposed controls and PTSD participants was measured with MEG as they listened to individualized trauma narratives as well as to a neutral narrative and as they imagined the narrative in detail. Source localization analysis by frequency bands was conducted in order to map neural generators of oscillatory activity.

RESULTS Elicitation of traumatic memories resulted in a distinct neural pattern in PTSD patients compared to healthy trauma-exposed individuals. In response to

trauma scripts PTSD patients showed increases in high-gamma band power in visual areas, increased frontal and temporal theta as well as prefrontal alpha and medial temporal beta power relative to neutral scripts.

CONCLUSIONS Results suggest that when recollecting and imagining traumatic memories PTSD patients attempt to engage control or inhibition mechanisms. However, these are either not successfully recruited or inefficient leading to heightened responses and recollection.

SIGNIFICANCE Investigating the oscillatory neural dynamics of PTSD patients can help us better understand the processes underlying trauma re-experiencing.

Keywords: Imagery, Magnetoencephalography, Oscillatory brain activity, Post traumatic stress disorder

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2022), Vol. 139 (35537254) (0 citations)

Classification of posttraumatic stress disorder and related outcomes in women veterans using magnetoencephalography (2022)

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ABSTRACT Women veterans represent a unique population whose experiences and neurobiology differ from that of their male counterparts. Thus, while previous research has demonstrated the utility of synchronous neural interactions (SNI) as a biomarker of posttraumatic stress disorder (PTSD) in male veterans, the utility of SNI as a biomarker of PTSD in women veterans is unclear. Here we extend that line of research to evaluate classification of women veterans with and without PTSD and other trauma-related outcomes based on functional connectivity using magnetoencephalography (MEG). A total of 121 U.S. women veterans completed diagnostic interviews and underwent a task-free MEG scan from which SNI was computed. Linear discriminant analysis was used to classify PTSD and control groups according to SNI. That discriminant function was then used to classify each individual in the partial recovery and full recovery diagnostic groups as PTSD or control. All individuals were classified correctly (100% accuracy) according to their SNI in their PTSD and control groups. Seventy-seven percent of the full recovery group and 69% of the partial recovery group were classified as control. Individual staging in PTSD recovery was captured by the Mahalanobis D[2] distances from the center of the control and PTSD centroid clusters. These findings provide compelling evidence supporting the utility of task-free SNI as a biomarker of PTSD and related outcomes in women veterans.

Keywords: Biomarker, Classification, Magnetoencephalography, Posttraumatic stress disorder, Recovery, Veterans

Experimental brain research (2022), Vol. 240, No. 4 (35133447) (2 citations)

Alterations in the Topology of Functional Connectomes Are Associated with Post-Traumatic Stress Disorder and Blast-Related Mild Traumatic Brain Injury in Combat Veterans (2021)

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ABSTRACT Post-traumatic stress disorder (PTSD) is a common condition in post-deployment service members (SM). SMs of the conflicts in Iraq and Afghanistan also frequently experience traumatic brain injury (TBI) and exposure to blasts during deployments. This study evaluated the effect of these conditions and experiences on functional brain connectomes in post-deployment, combat-exposed veterans. Functional brain connectomes were created using 5-min resting-state magnetoencephalography data. Well-established clinical interviews determined current PTSD diagnosis, as well as deployment-acquired mild TBI and history of exposure to blast. Linear regression examined the effect of these conditions on functional brain connectomes beyond covariates. There were significant interactions between blast-related mild TBI and PTSD after correction for multiple comparisons including number of nodes (non-standardized parameter estimate [PE] = -12.47), average degree (PE = 0.05), and connection strength (PE = 0.05). A main effect of blast-related mild TBI was observed on the threshold level. These results demonstrate a distinct functional connectome presentation associated with the presence of both blast-related mild TBI and PTSD. These findings suggest the possibility that blast-related mild TBI alterations in functional brain connectomes affect the presentation or progression of recovery from PTSD. The current results offer mixed support for hyper-connectivity in the chronic phase of deployment TBI.

Keywords: PTSD, TBI, connectome, deployment, network

Journal of neurotrauma (2021), Vol. 38, No. 22 (34435885) (4 citations)

Post-traumatic stress disorder is associated with alterations in evoked cortical activation during visual recognition of scenes (2021)

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ABSTRACT We recorded magnetoencephalography data during a visual recognition task in participants with combat exposure (n = 40, age: 41.2 ± 7.2 years) to investigate the relationship between the evoked brain activity, behavioral performance, and the severity of their post-traumatic stress symptoms assessed using the PTSD Check List for DSM V version (PCL-5). In an initial study session, participants were presented with a series of images of outdoor scenes and were instructed to study the images for an upcoming recognition test. In a subsequent session, the original images were shown intermixed with novel images while participants performed the recognition task. PCL-5 scores were negatively correlated with discrimination performance and with the recognition accuracy for original images. During the recognition session, higher PCL-5 scores were associated with reduced relative power of the evoked response to original images from 100 ms to 300 ms following the image onset over a distributed brain network including the bilateral inferior frontal gyri, left middle frontal gyrus, left supramarginal gyrus, right precuneus and the bilateral superior temporal gyri. These findings indicate that the lower recognition performance in participants with higher PTSD symptom severity is associated with altered cortical activity in brain regions that are known to play a role in the elaboration on visual cues that supports recollection.

Keywords: Magnetoencephalography, Post-traumatic stress disorder, Predictive coding, Recognition memory

NeuroImage. Clinical (2021), Vol. 31 (34284337) (0 citations)

Teasing apart trauma: neural oscillations differentiate individual cases of mild traumatic brain injury from post-traumatic stress disorder even when symptoms overlap (2021)

Zhang, Jing; Emami, Zahra; Safar, Kristina; McCunn, Patrick; Richardson, J Don; Rhind, Shawn G; da Costa, Leodante; Jetly, Rakesh; Dunkley, Benjamin T

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ABSTRACT Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are highly prevalent and closely related disorders. Affected individuals often exhibit substantially overlapping symptomatology - a major challenge for differential diagnosis in both military and civilian contexts. According to our symptom assessment, the PTSD group exhibited comparable levels of concussion symptoms and severity to the mTBI group. An objective and reliable system to uncover the key neural signatures differentiating these disorders would be an important step towards translational and applied clinical use. Here we explore use of MEG (magnetoencephalography)-multivariate statistical learning analysis in identifying the neural features for differential PTSD/mTBI characterisation. Resting state MEG-derived regional neural activity and coherence (or functional connectivity) across seven canonical neural oscillation frequencies (delta to high gamma) were used. The selected features were consistent and largely confirmatory with previously established neurophysiological markers for the two disorders. For regional power from theta, alpha and high gamma bands, the amygdala, hippocampus and temporal areas were identified. In line with regional activity, additional connections within the occipital, parietal and temporal regions were selected across a number of frequency bands. This study is the first to employ MEG-derived neural features to reliably and differentially stratify the two disorders in a multi-group context. The features from alpha and beta bands exhibited the best classification performance, even in cases where distinction by concussion symptom profiles alone were extremely difficult. We demonstrate the potential of using 'invisible' neural indices of brain functioning to understand and differentiate these debilitating conditions.

Translational psychiatry (2021), Vol. 11, No. 1 (34088901) (2 citations)

Predicting PTSD severity using longitudinal magnetoencephalography with a multi-step learning framework (2020)

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ABSTRACT Objective. The present study explores the effectiveness of incorporating temporal information in predicting post-traumatic stress disorder (PTSD) severity using magnetoencephalography (MEG) imaging data. The main objective was to assess the relationship between longitudinal MEG functional connectome data, measured across a variety of neural oscillatory frequencies and collected at two timepoints (Phase I and II), against PTSD severity captured at the later time point.Approach. We used an in-house developed informatics solution, featuring a two-step process featuring pre-learn feature selection (CV-SVR-rRF-FS, cross-validation with support vector regression (SVR) and recursive random forest feature selection) and deep learning (long-short term memory recurrent neural network, LSTM-RNN) techniques.Main results. The pre-learn step selected a small number of functional connections (or edges) from Phase I MEG data associated with Phase II PTSD severity, indexed using the PTSD CheckList (PCL) score. This strategy identified the functional edges affected by traumatic exposure and indexed disease severity, either permanently or evolving dynamically over time, for optimal predictive performance. Using the selected functional edges, LSTM modelling was used to incorporate the Phase II MEG data into longitudinal regression models. Single timepoint (Phase I and Phase

II MEG data) SVR models were generated for comparison. Assessed with holdout test data, alpha and high gamma bands showed enhanced predictive performance with the longitudinal models comparing to the Phase I single timepoint models. The best predictive performance was observed for lower frequency ranges compared to the higher frequencies (low gamma), for both model types.Significance. This study identified the neural oscillatory signatures that benefited from additional temporal information when estimating the outcome of PTSD severity using MEG functional connectome data. Crucially, this approach can similarly be applied to any other mental health challenge, using this effective informatics foundation for longitudinal tracking of pathological brain states and predicting outcome with a MEG-based neurophysiology imaging system.

Keywords: functional connectivity, long short-term memory, neuroimaging, neuropsychiatric disorders, neuroscience, post-traumatic stress disorder, recurrent neural network

Journal of neural engineering (2020), Vol. 17, No. 6 (33166947) (1 citation)

Cumulative Risk on Oxytocin-Pathway Genes Impairs Default Mode Network Connectivity in Trauma-Exposed Youth (2020)

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ABSTRACT Background: Although the default mode network (DMN) is a core network essential for brain functioning, little is known about its developmental trajectory, particularly on factors associated with its coherence into a functional network. In light of adult studies indicating DMN's susceptibility to stress-related conditions, we examined links between variability on oxytocin-pathway genes and DMN connectivity in youth exposed to chronic war-related trauma Methods: Following a cohort of war-exposed children from early childhood, we imaged the brains of 74 preadolescents (age 11-13 years; 39 war-exposed) during rest using magnetoencephalography (MEG). A cumulative risk index on oxytocin-pathway genes was constructed by combining single nucleotide polymorphisms on five genes previously linked with social deficits and psychopathology; OXTR rs1042778, OXTR rs2254298, OXTRrs53576, CD38 rs3796863, and AVPR1A RS3. Avoidant response to trauma reminders in early childhood and anxiety disorders in late childhood were assessed as predictors of disruptions to DMN theta connectivity. Results: Higher vulnerability on oxytocin-pathway genes predicted greater disruptions to DMN theta connectivity. Avoidant symptoms in early childhood and generalized anxiety disorder in later childhood were related to impaired DMN connectivity. In combination, stress exposure, oxytocin-pathway genes, and stress-related symptoms explained 24.6% of the variance in DMN connectivity, highlighting the significant effect of stress on the maturing brain. Conclusions: Findings are the first to link the oxytocin system and maturation of the DMN, a core system sustaining autobiographical memories, alteration of intrinsic and extrinsic attention, mentalization, and sense of self. Results suggest that oxytocin may buffer the effects of chronic early stress on the DMN, particularly theta rhythms that typify the developing brain.

Keywords: OXTR, anxiety disorders, genetics, longitudinal studies, magnetoencephalography, trauma exposure

Frontiers in endocrinology (2020), Vol. 11 (32528417) (8 citations)

Magnetoencephalography for Mild Traumatic Brain Injury and Posttraumatic Stress Disorder (2020)

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ABSTRACT Mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD) are leading causes of sustained physical, cognitive, emotional, and behavioral deficits in the general population, active-duty military personnel, and veterans. However, the underlying pathophysiology of mTBI/PTSD and the mechanisms that support functional recovery for some, but not all individuals is not fully understood. Conventional MR imaging and computed tomography are generally negative in mTBI and PTSD, so there is interest in the development of alternative evaluative strategies. Of particular note are magnetoencephalography (MEG) -based methods, with mounting evidence that MEG can provide sensitive biomarkers for abnormalities in mTBI and PTSD.

Keywords: Functional connectivity, GABA-ergic, Gamma wave, Posttraumatic stress disorder, Slow wave, Traumatic brain injury

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336405) (4 citations)

Classifying post-traumatic stress disorder using the magnetoencephalographic connectome and machine learning (2020)

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ABSTRACT Given the subjective nature of conventional diagnostic methods for post-traumatic stress disorder (PTSD), an objectively measurable biomarker is highly desirable; especially to clinicians and researchers. Macroscopic neural circuits measured using magnetoencephalography (MEG) has previously been shown to be indicative of the PTSD phenotype and severity. In the present study, we employed a machine learning-based classification framework using MEG neural synchrony to distinguish combat-related PTSD from trauma-exposed controls. Support vector machine (SVM) was used as the core classification algorithm. A recursive random forest feature selection step was directly incorporated in the nested SVM cross validation process (CV-SVM-rRF-FS) for identifying the most important features for PTSD classification. For the five frequency bands tested, the CV-SVM-rRF-FS analysis selected the minimum numbers of edges per frequency that could serve as a PTSD signature and be used as the basis for SVM modelling. Many of the selected edges have been reported previously to be core in PTSD pathophysiology, with frequency-specific patterns also observed. Furthermore, the independent partial least squares discriminant analysis suggested low bias in the machine learning process. The final SVM models built with selected features showed excellent PTSD classification performance (area-under-curve value up to 0.9). Testament to its robustness when distinguishing individuals from a heavily traumatised control group, these developments for a classification model for PTSD also provide a comprehensive machine learning-based computational framework for classifying other mental health challenges using MEG connectome profiles.

Scientific reports (2020), Vol. 10, No. 1 (32246035) (15 citations)

Altered modulation of beta band oscillations during memory encoding is predictive of lower subsequent recognition performance in post-traumatic stress disorder (2020)

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ABSTRACT We studied the relationship between electrophysiological markers of memory encoding, subsequent recognition performance, and severity of PTSD symptoms in service members with combat exposure (n = 40, age: 41.2 ± 7.2 years) and various levels of PTSD symptom severity assessed using the PTSD Check List for DSM V version (PCL-5). Brain activity was recorded using magnetoencephalography during a serial presentation of 86 images of outdoor scenes that were studied by participants for an upcoming recognition test. In a second session, the original images were shown intermixed with an equal number of novel images while participants performed the recognition task. Participants recognized 76.0% ± 12.1% of the original images and correctly categorized as novel 89.9% ± 7.0% of the novel images. A negative correlation was present between PCL-5 scores and discrimination performance (Spearman rs = -0.38, p = 0.016). PCL-5 scores were also negatively correlated with the recognition accuracy for original images (rs = -0.37, p = 0.02). Increases in theta and gamma power and decreases in alpha and beta power were observed over distributed brain networks during memory encoding. Higher PCL-5 scores were associated with less suppression of beta band power in bilateral ventral and medial temporal regions and in the left orbitofrontal cortex. These regions also showed positive correlations between the magnitude of suppression of beta power during encoding and subsequent recognition accuracy. These findings indicate that the lower recognition performance in participants with greater PTSD symptom severity may be due in part to ineffective encoding reflected in altered modulation of beta band oscillatory activity.

Keywords: Beta band oscillations, Magnetoencephalography, Memory encoding, Post-traumatic stress disorder

NeuroImage. Clinical (2020), Vol. 25 (31951934) (4 citations)

Schizophrenia

Abnormal Information Flow in Schizophrenia Is Linked to Psychosis (2022)

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BACKGROUND AND HYPOTHESIS Prior research has shown that patients with schizophrenia (SZ) show disruption in brain network connectivity that is thought to underlie their cognitive and psychotic symptoms. However, most studies examining functional network disruption in schizophrenia have focused on the temporally correlated coupling of the strength of network connections. Here, we move beyond correlative metrics to assay causal computations of connectivity changes in directed neural information flow, assayed from a neural source to a target in SZ.

STUDY DESIGN This study describes a whole-brain magnetoencephalography-imaging approach to examine causal computations of connectivity changes in directed neural information flow between brain regions during resting states, quantified by phase-transfer entropy (PTE) metrics, assayed from a neural source to an endpoint, in 21 SZ compared with 21 healthy controls (HC), and associations with cognitive and clinical psychotic symptoms in SZ.

STUDY RESULTS We found that SZ showed significant disruption in information flow in alpha (8-12 Hz) and beta (12-30 Hz) frequencies, compared to HC. Reduced information flow in alpha frequencies from the precuneus to the medio-ventral occipital cortex was associated with more severe clinical psychopathology (ie, positive psychotic symptoms), while reduced information flow between insula and middle temporal gyrus was associated with worsening cognitive symptoms.

CONCLUSIONS The present findings highlight the importance of delineating dysfunction in neural information flow in specific oscillatory frequencies between distinct regions that underlie the cognitive and psychotic symptoms in SZ, and provide potential neural biomarkers that could lead to innovations in future neuromodulation treatment development.

Keywords: phase, psychotic symptoms, resting, state MEG, transfer entropy

Schizophrenia bulletin (2022), Vol. 48, No. 6 (36073155) (0 citations)

Neuronal imbalance of excitation and inhibition in schizophrenia: a scoping review of gamma-band ASSR findings (2022)

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ABSTRACT Recent empirical findings suggest that altered neural synchronization, which is hypothesized to be associated with an imbalance of excitatory (E) and inhibitory (I) neuronal activities, may underlie a core pathophysiological mechanism in patients with schizophrenia. The auditory steady-state response (ASSR) examined by electroencephalography (EEG) and magnetoencephalography (MEG) has been proposed as a potential biomarker for evaluating altered neural synchronization in schizophrenia. For this review, we performed a comprehensive literature search for papers published between 1999 and 2021 examining ASSRs in patients with schizophrenia. Almost all EEG-ASSR studies reported gamma-band ASSR reductions, especially to 40-Hz stimuli both in power and/or phase synchronization in chronic and first-episode schizophrenia. In addition, similar to EEG-ASSR findings, MEG-ASSR deficits to 80-Hz stimuli (high gamma) have been reported in patients with schizophrenia. Moreover, the 40-Hz ASSR is likely to be a predictor of the onset of schizophrenia. Notably, increased spontaneous (or ongoing) broadband (30-100 Hz) gamma power has been reported during ASSR tasks, which resembles the increased spontaneous gamma activity reported in animal models of E/I imbalance. Further research on ASSRs and evoked and spontaneous gamma oscillations is expected to elucidate the pathophysiology of schizophrenia with translational implications.

Keywords: E/I imbalance, EEG/MEG, auditory steady-state response, biomarker, gamma oscillations, schizophrenia

Psychiatry and clinical neurosciences (2022), Vol. 76, No. 12 (36069299) (4 citations)

Load-dependent functional connectivity deficits during visual working memory in first-episode psychosis (2022)

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INTRODUCTION Aberrant network connectivity is a core deficit in schizophrenia and may underlie many of its associated cognitive deficits. Previous work in first-episode schizophrenia spectrum illness (FESz) suggests preservation of working memory network function during low-load conditions with dysfunction emerging as task complexity increases. This study assessed visual network connectivity and its contribution to load-dependent working memory impairments.

METHODS Magnetoencephalography was recorded from 35 FESz and 28 matched controls (HC) during a lateralized change detection task. Impaired alpha desynchronization was previously identified within bilateral dorsal occipital (Occ) regions. Here, whole-brain alpha-band connectivity was examined using phase-locking (PLV) and bilateral Occ as connectivity seeds. Load effects on connectivity were assessed across participants, and PLV modulation within networks was compared between groups.

RESULTS Occ exhibited significant load modulated connectivity with six regions (FDR-corrected). HC exhibited PLV enhancement with load in all connections. FESz failed to show PLV modulation between right Occ and left inferior frontal gyrus, lateral occipito-temporal sulcus, and anterior intermediate parietal sulcus. Smaller PLVs in all three network connections during both memory load conditions were associated with increased reality distortion in FESz (FDR-corrected.) CONCLUSION: Examination of functional connectivity across the visual working memory network in FESz revealed an inability to enhance communication between perceptual and executive networks in response to increasing cognitive demands. Furthermore, the degree of network communication impairment was associated with positive symptoms. These findings provide insights into the nature of brain dysconnectivity and its contribution to symptoms in early psychosis and identify potential targets for future interventions.

Keywords: First-episode psychosis, Functional connectivity, Magnetoencephalography, Reality distortion, Visual working memory

Journal of psychiatric research (2022), Vol. 153 (35820225) (1 citation)

Altered Brain Criticality in Schizophrenia: New Insights From Magnetoencephalography (2022)

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ABSTRACT Schizophrenia has a complex etiology and symptomatology that is difficult to untangle. After decades of research, important advancements toward a central biomarker are still lacking. One of the missing pieces is a better understanding of how non-linear neural dynamics are altered in this patient population. In this study, the resting-state neuromagnetic signals of schizophrenia patients and healthy controls were analyzed in the framework of criticality. When biological systems like the brain are in a state of criticality, they are thought to be functioning at maximum efficiency (e.g., optimal communication and storage of information) and with maximum adaptability to incoming information. Here, we assessed the self-similarity and multifractality of resting-state brain signals recorded with magnetoencephalography in patients with schizophrenia patients and in matched controls. Schizophrenia patients had similar, although attenuated, patterns of self-similarity and multifractality values. Statistical tests showed that patients had higher values of self-similarity than controls in fronto-temporal regions, indicative of more regularity and memory in the signal. In contrast, patients had less multifractality than controls in the parietal and occipital regions, indicative of less diverse singularities and reduced variability in the signal. In addition, supervised machine-learning, based on logistic regression, successfully discriminated the two groups using measures of self-similarity and multifractality as features. Our results provide new insights into the baseline cognitive functioning of schizophrenia patients by identifying key alterations of criticality properties in their resting-state brain data.

Keywords: complexity, criticality, machine-learning, magnetoencephalography, multifractal analysis, resting-state, scale-free dynamics

Frontiers in neural circuits (2022), Vol. 16 (35418839) (4 citations)

Disrupted local beta band networks in schizophrenia revealed through graph analysis: A magnetoencephalography study (2022)

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AIMS Schizophrenia (SZ) is characterized by psychotic symptoms and cognitive impairment, and is

hypothesized to be a 'dysconnection' syndrome due to abnormal neural network formation. Although numerous studies have helped elucidate the pathophysiology of SZ, many aspects of the mechanism underlying psychotic symptoms remain unknown. This study used graph theory analysis to evaluate the characteristics of the resting-state network (RSN) in terms of microscale and macroscale indices, and to identify candidates as potential biomarkers of SZ. Specifically, we discriminated topological characteristics in the frequency domain and investigated them in the context of psychotic symptoms in patients with SZ.

METHODS We performed graph theory analysis of electrophysiological RSN data using magnetoencephalography to compare topological characteristics represented by microscale (degree centrality and clustering coefficient) and macroscale (global efficiency, local efficiency, and small-worldness) indices in 29 patients with SZ and 38 healthy controls. In addition, we investigated the aberrant topological characteristics of the RSN in patients with SZ and their relationship with SZ symptoms.

RESULTS SZ was associated with a decreased clustering coefficient, local efficiency, and small-worldness, especially in the high beta band. In addition, macroscale changes in the low beta band are closely associated with negative symptoms.

CONCLUSIONS The local networks of patients with SZ may disintegrate at both the microscale and macroscale levels, mainly in the beta band. Adopting an electrophysiological perspective of SZ as a failure to form local networks in the beta band will provide deeper insights into the pathophysiology of SZ as a 'dysconnection' syndrome.

Keywords: beta band, graph theory, magnetoencephalography, resting-state network, schizophrenia

Psychiatry and clinical neurosciences (2022), Vol. 76, No. 7 (35397141) (0 citations)

Auditory driven gamma synchrony is associated with cortical thickness in widespread cortical areas (2022)

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OBJECTIVE Gamma synchrony is a fundamental functional property of the cerebral cortex, impaired in multiple neuropsychiatric conditions (i.e. schizophrenia, Alzheimer's disease, stroke etc.). Auditory stimulation in the gamma range allows to drive gamma synchrony of the entire cortical mantle and to estimate the efficiency of the mechanisms sustaining it. As gamma synchrony depends strongly on the interplay between parvalbumin-positive interneurons and pyramidal neurons, we hypothesize an association between cortical thickness and gamma synchrony. To test this hypothesis, we employed a combined magnetoencephalography (MEG) - Magnetic Resonance Imaging (MRI) study.

METHODS Cortical thickness was estimated from anatomical MRI scans. MEG measurements related to exposure of 40 Hz amplitude modulated tones were projected onto the cortical surface. Two measures of cortical synchrony were considered: (a) inter-trial phase consistency at 40 Hz, providing a vertex-wise estimation of gamma synchronization, and (b) phase-locking values between primary auditory cortices and whole cortical mantle, providing a measure of long-range cortical synchrony. A correlation between cortical thickness and synchronization measures was then calculated for 72 MRI-MEG scans.

RESULTS Both inter-trial phase consistency and phase locking values showed a significant positive correlation with cortical thickness. For inter-trial phase consistency, clusters of strong associations were found in the temporal and frontal lobes, especially in the bilateral auditory and pre-motor cortices. Higher phase-locking values corresponded to higher cortical thickness in the frontal, temporal, occipital and parietal lobes.

DISCUSSION AND CONCLUSIONS In healthy subjects, a thicker cortex corresponds to higher gamma synchrony and connectivity in the primary auditory cortex and beyond, likely reflecting underlying cell density involved in gamma circuitries. This result hints towards an involvement of gamma synchrony together with underlying brain structure in brain areas for higher order cognitive functions. This study contributes to the understanding of inherent cortical functional and structural brain properties, which might in turn constitute the basis for the definition of useful biomarkers in patients showing aberrant gamma synchronization.

Keywords: Auditory Steady State Responses (ASSR), Cerebral cortex, Cortical thickness, Gamma, Magnetoencephalography (MEG), Synchrony

NeuroImage (2022), Vol. 255 (35390460) (2 citations)

Genetic risk for schizophrenia is associated with altered visually-induced gamma band activity: evidence from a population sample stratified polygenic risk (2021)

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ABSTRACT Gamma oscillations (30-90 Hz) have been proposed as a signature of cortical visual information processing, particularly the balance between excitation and inhibition, and as a biomarker of neuropsychiatric diseases. Magnetoencephalography (MEG) provides highly reliable visual-induced gamma oscillation estimates, both at sensor and source level. Recent studies have reported a deficit of visual gamma activity in schizophrenia patients, in medication naive subjects, and high-risk clinical participants, but the genetic contribution to such a deficit has remained unresolved. Here, for the first time, we use a genetic risk score approach to assess the relationship between genetic risk for schizophrenia and visual gamma activity in a population-based sample drawn from a birth cohort. We compared visual gamma activity in a group (N = 104) with a high genetic risk profile score for schizophrenia (SCZ-PRS) to a group with low SCZ-PRS (N = 99). Source-reconstructed V1 activity was extracted using beamformer analysis applied to MEG recordings using individual MRI scans. No group differences were found in the induced gamma peak amplitude or peak frequency. However, a non-parametric statistical contrast of the response spectrum revealed more robust group differences in the amplitude of high-beta/gamma power across the frequency range, suggesting that overall spectral shape carries important biological information beyond the individual frequency peak. Our findings show that changes in gamma band activity correlate with liability to schizophrenia and suggest that the index changes to synaptic function and neuronal firing patterns that are of pathophysiological relevance rather than consequences of the disorder.

Translational psychiatry (2021), Vol. 11, No. 1 (34785639) (0 citations)

The beta component of gamma-band auditory steady-state responses in patients with schizophrenia (2021)

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ABSTRACT The mechanisms underlying circuit dysfunctions in schizophrenia (SCZ) remain poorly understood. Auditory steady-state responses (ASSRs), especially in the gamma and beta band, have been suggested as a potential biomarker for SCZ. While the reduction of 40 Hz power for 40 Hz drive has been well established and replicated in SCZ patients, studies are inconclusive when it comes to an increase in 20 Hz power during 40 Hz drive. There might be several factors explaining the inconsistencies, including differences in the sensitivity of the recording modality (EEG vs MEG), differences in stimuli (click-trains vs amplitude-modulated tones) and large differences in the amplitude of the stimuli. Here, we used a computational model of ASSR deficits in SCZ and explored the effect of three SCZ-associated microcircuit alterations: reduced GABA activity, increased GABA decay times and NMDA receptor hypofunction. We investigated the effect of input strength on gamma (40 Hz) and beta (20 Hz) band power during gamma ASSR stimulation and saw that the pronounced increase in beta power during gamma stimulation seen experimentally could only be reproduced in the model when GABA decay times were increased and only for a specific range of input strengths. More specifically, when the input was in this specific range, the rhythmic drive at 40 Hz produced a strong 40 Hz rhythm in the control network; however, in the 'SCZ-like' network, the prolonged inhibition led to a so-called 'beat-skipping', where the network would only strongly respond to every other input. This mechanism was responsible for the emergence of the pronounced 20 Hz beta peak in the power spectrum. The other two microcircuit alterations were not able to produce a substantial 20 Hz component but they further narrowed the input strength range for which the network produced a beta component when combined with increased GABAergic decay times. Our finding that the beta component only existed for a specific range of input strengths might explain the seemingly inconsistent reporting in experimental studies and suggests that future ASSR studies should systematically explore different amplitudes of their stimuli. Furthermore, we provide a mechanistic link between a microcircuit alteration and an electrophysiological marker in schizophrenia and argue that more complex ASSR stimuli are needed to disentangle the nonlinear interactions of microcircuit alterations. The computational modelling approach put forward here is ideally suited to facilitate the development of such stimuli in a theory-based fashion.

Scientific reports (2021), Vol. 11, No. 1 (34650135) (0 citations)

Current findings and perspectives on aberrant neural oscillations in schizophrenia (2021)

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ABSTRACT There is now consistent evidence that neural oscillation at low- and high-frequencies constitute an important aspect of the pathophysiology of schizophrenia. Specifically, impaired rhythmic activity may underlie the deficit to generate coherent cognition and behavior, leading to the characteristic symptoms of psychosis and cognitive deficits. Importantly, the generating mechanisms of neural oscillations are relatively well-understood and thus enable the targeted search for the underlying circuit impairments and novel treatment targets. In the following review, we will summarize and assess the evidence for aberrant rhythmic activity in schizophrenia through evaluating studies that have utilized Electro/Magnetoencephalography to examine neural oscillations during sensory and cognitive tasks as well as during resting-state measurements. These data will be linked to current evidence from post-mortem, neuroimaging, genetics, and animal models that have implicated deficits in GABAergic interneurons

and glutamatergic neurotransmission in oscillatory deficits in schizophrenia. Finally, we will highlight methodological and analytical challenges as well as provide recommendations for future research.

Keywords: EEG, MEG, neural oscillation, schizophrenia

Psychiatry and clinical neurosciences (2021), Vol. 75, No. 12 (34558155) (15 citations)

Fronto-parietal network function during cued visual search in the first-episode schizophrenia spectrum (2021)

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ABSTRACT Cognitive impairments account for significant morbidity in schizophrenia and are present at disease onset. Controlled processes are particularly susceptible and may contribute to pervasive selective attention deficits. The present study assessed fronto-parietal attention network (FPAN) functioning during cue presentation on a visual search task in first-episode schizophrenia spectrum patients (FE) and its relation to symptom burden and community functioning. Brain activity was recorded with magnetoencephalography from 38 FE and 38 healthy controls (HC) during blocks of pop-out and serial search target detection. Activity during cue presentation was compared between groups across bilateral FPAN regions (frontal eye fields (FEF), inferior frontal gyrus (IFG), midcingulate cortex (MCC), and intraparietal sulcus (IPS)). FE exhibited greater right hemisphere IFG activity despite worse performance relative to HC. Performance and FPAN activity were not correlated in HC. Among FE, however, stronger activity within right hemisphere FEF and IFG was associated with faster responses. Stronger right IPS and left IFG activity in patients was also associated with reduced negative symptoms and improved community functioning, respectively. Increased reliance on the FPAN for task completion suggests an inefficient cognitive control network and might reflect a compensation for impaired attentional deployment during target detection, a strategy employed by those with less severe illness. These findings represent a critical step towards identifying the neural substrates of negative symptoms and impaired neurocognition at disease onset.

Keywords: Attention, First-episode, Fronto-parietal attention network, Magnetoencephalography, Schizophrenia

Journal of psychiatric research (2021), Vol. 141 (34304038) (3 citations)

Impaired neural replay of inferred relationships in schizophrenia (2021)

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ABSTRACT An ability to build structured mental maps of the world underpins our capacity to imagine relationships between objects that extend beyond experience. In rodents, such representations are supported by sequential place cell reactivations during rest, known as replay. Schizophrenia is proposed to reflect a compromise in structured mental representations, with animal models reporting abnormalities in hippocampal replay and associated ripple activity during rest. Here, utilizing magnetoencephalography (MEG), we tasked patients with schizophrenia and control participants to infer unobserved relationships between objects by reorganizing visual experiences containing these objects. During a post-task rest session, controls exhibited fast spontaneous neural reactivation of presented objects that replayed inferred relationships. Replay was coincident with increased ripple power in hippocampus. Patients showed both reduced replay and augmented ripple power relative to controls, convergent with findings in animal models. These abnormalities are linked to impairments in behavioral acquisition and subsequent neural representation of task structure.

Keywords: cognitive map, mental simulation, model-based inference, psychosis, schema

Cell (2021), Vol. 184, No. 16 (34197734) (17 citations)

Long range temporal correlations (LRTCs) in MEG-data during emerging psychosis: Relationship to symptoms, medication-status and clinical trajectory (2021)

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ABSTRACT Long-Range Temporal Correlations (LRTCs) index the capacity of the brain to optimally process information. Previous research has shown that patients with chronic schizophrenia present altered LRTCs at alpha and beta oscillations. However, it is currently unclear at which stage of schizophrenia aberrant LRTCs emerge. To address this question, we investigated LRTCs in resting-state magnetoencephalographic (MEG) recordings obtained from patients with affective disorders and substance abuse (clinically at low-risk of psychosis, CHR-N), patients at clinical high-risk of psychosis (CHR-P) (n = 115), as well as patients with a first episode (FEP) (n = 25). Matched healthy controls (n = 47) served as comparison group. LRTCs were obtained for frequencies from 4 to 40 Hz and correlated with clinical and neuropsychological data. In addition, we examined the relationship between LRTCs and transition to psychosis in CHR-P participants, and the relationship between LRTC and antipsychotic medication in FEP participants. Our results show that participants from the clinical groups have similar LRTCs to controls. In addition, LRTCs did not correlate with clinical and neurocognitive variables across participants nor did LRTCs predict transition to psychosis. Therefore, impaired LRTCs do not reflect a feature in the clinical trajectory of psychosis. Nevertheless, reduced LRTCs in the beta-band over posterior sensors of medicated FEP participants indicate that altered LRTCs may appear at the onset of the illness. Future studies are needed to elucidate the role of anti-psychotic medication in altered LRTCs.

Keywords: Biomarker, Emerging-psychosis, Longrange-temporal-correlations, Magnetoencephalography, Oscillations, Schizophrenia

NeuroImage. Clinical (2021), Vol. 31 (34130193) (3 citations)

Patient, interrupted: MEG oscillation dynamics reveal temporal dysconnectivity in schizophrenia (2020)

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ABSTRACT Current theories of schizophrenia emphasize the role of altered information integration as the core dysfunction of this illness. While ample neuroimaging evidence for such accounts comes from investigations of spatial connectivity, understanding temporal disruptions is important to fully capture the essence of dysconnectivity in schizophrenia. Recent electrophysiology studies suggest that long-range temporal correlation (LRTC) in the amplitude dynamics of neural oscillations captures the integrity of transferred information in the healthy brain. Thus, in this study, 25 schizophrenia patients and 25 controls (8 females/group) were recorded during two five-minutes of resting-state magnetoencephalography (once with eyes-open and once with eyes-closed). We used source-level analyses to investigate temporal dysconnectivity in patients by characterizing LRTCs across cortical and sub-cortical brain regions. In addition to standard statistical assessments, we applied a machine learning framework using support vector machine to evaluate the discriminative power of LRTCs in identifying patients from healthy controls. We found that neural oscillations in schizophrenia patients were characterized by reduced signal memory and higher variability across time, as evidenced by cortical and subcortical attenuations of LRTCs in the alpha and beta frequency bands. Support vector machine significantly classified participants using LRTCs in key limbic and paralimbic brain areas, with decoding accuracy reaching 82%. Importantly, these brain regions belong to networks that are highly relevant to the symptomology of schizophrenia. These findings thus posit temporal dysconnectivity as a hallmark of altered information processing in schizophrenia, and help advance our understanding of this pathology.

Keywords: Long-range-temporal-correlations, Machine-learning, Magnetoencephalography, Oscillations, Resting-state, Schizophrenia

NeuroImage. Clinical (2020), Vol. 28 (33395976) (4 citations)

Motor-related oscillatory activity in schizophrenia according to phase of illness and clinical symptom severity (2021)

Gascoyne, Lauren E; Brookes, Matthew J; Rathnaiah, Mohanbabu; Katshu, Mohammad Zia Ul Haq; Koelewijn, Loes; Williams, Gemma; Kumar, Jyothika; Walters, James T R; Seedat, Zelekha A; Palaniyappan, Lena; Deakin, J F William; Singh, Krish D; Liddle, Peter F; Morris, Peter G

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ABSTRACT Magnetoencephalography (MEG) measures magnetic fields generated by synchronised neural current flow and provides direct inference on brain electrophysiology and connectivity, with high spatial and temporal resolution. The movement-related beta decrease (MRBD) and the post-movement beta rebound (PMBR) are well-characterised effects in magnetoencephalography (MEG), with the latter having been shown to relate to long-range network integrity. Our previous work has shown that the PMBR is diminished (relative to controls) in a group of schizophrenia patients. However, little is known about how this effect might differ in patients at different stages of illness and degrees of clinical severity. Here, we extend our previous findings showing that the MEG derived PMBR abnormality in schizophrenia exists in 29 recent-onset and 35 established cases (i.e., chronic patients), compared to 42 control cases. In established cases, PMBR is negatively correlated with severity of disorganization symptoms. Further, using a hidden Markov model analysis, we show that transient pan-spectral oscillatory "bursts", which underlie the PMBR, differ between healthy controls and patients. Results corroborate that PMBR is associated with disorganization of mental activity in schizophrenia.

Keywords: Oscillatory bursts, Post-movement beta rebound, Psychosis, Schizophrenia, Transient beta events

NeuroImage. Clinical (2021), Vol. 29 (33340975) (7 citations)

Inefficient visual search strategies in the first-episode schizophrenia spectrum (2020)

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BACKGROUND Knowledge is lacking regarding deficits in selective attention and their underlying biological mechanisms during early stages of schizophrenia. The present study examined the N2pc, a neurophysiological index of covert spatial attention, and its cortical sources at first psychotic episode in the schizophrenia spectrum (FESz).

METHODS Neurophysiological responses measured simultaneously with magnetoencephalography (MEG) and electroencephalography (EEG) during pop-out and serial search tasks were compared between 32 FESz and 32 matched healthy controls (HC). Mean scalp-recorded N2pc was measured from a cluster of posterior-lateral EEG electrodes. Cortical source-resolved MEG activity contributing to the N2pc signal was derived for the intraparietal sulcus (IPS) and lateral occipital complex (LOC).

RESULTS Group differences in EEG N2pc varied by task demand. FESz exhibited reduced N2pc amplitude during pop-out ($p < .01$), but not serial search ($p = .11$). Furthermore, group differences in N2pc-related MEG cortical activity varied by task demand and cortical region. Compared to HC, FESz exhibited greater IPS during serial search ($p < .01$).

DISCUSSION Reductions in EEG N2pc amplitude indicate an impairment of visuo-spatial attention evident

at an individual's first psychotic episode, specifically during conditions emphasizing bottom-up processing. Examination of its cortical sources with MEG revealed that, compared to HC, FESz engaged parietal structures to a greater extent during the serial search condition. This pattern suggests a less efficient, more resource intensive strategy employed by FESz in response to a minimal demand on attention. The greater reliance on this controlled attentional network may negatively impact real-world functions with much greater complexity and attentional demands.

Keywords: First-episode, Magnetoencephalography, N2pc, Schizophrenia spectrum, Selective attention, Visual search

Schizophrenia research (2020), Vol. 224 (33097368) (5 citations)

Lateralized evoked responses in parietal cortex demonstrate visual short-term memory deficits in first-episode schizophrenia (2020)

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ABSTRACT Working memory dysfunction may be central to neurocognitive deficits in schizophrenia. Maintenance of visual information in working memory, or visual short-term memory (vSTM), is linked to general cognitive dysfunction and predicts functional outcome. Lateralized change-detection tasks afford investigation of the contralateral delay activity (CDA), a useful tool for investigating vSTM dysfunction. Previous work suggests "hyperfocusing" of attention in schizophrenia, such that CDA is increased when a single item is maintained in vSTM but reduced for multiple items. If observed early in the disease, vSTM dysfunction may be a key feature of schizophrenia or target for intervention. We investigated CDA during lateralized vSTM of one versus three items using sensor-level electroencephalography and source-level magnetoencephalography in 26 individuals at their first episode of schizophrenia-spectrum psychosis (FESz) and 26 matched healthy controls. FESz were unable to modulate CDA with increased memory load - high-load CDA was reduced and low-load CDA was increased compared to controls. Further, sources of CDA in posterior parietal cortex were reduced in FESz and indices of working memory were correlated with neurocognitive deficits and symptom severity. These results support working memory maintenance dysfunction as a central and early component to the disorder. Targeted intervention focusing on vSTM deficits may be warranted to alleviate downstream effects of this disability.

Keywords: Contralateral delay activity, Electroencephalography, First-episode schizophrenia, Magnetoencephalography, Visual short-term memory, Working memory

Journal of psychiatric research (2020), Vol. 130 (32866678) (6 citations)

The Visual Word Form Area compensates for auditory working memory dysfunction in schizophrenia (2020)

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ABSTRACT Auditory working memory impairments feature prominently in schizophrenia. However, the existence of altered and perhaps compensatory neural dynamics, sub-serving auditory working memory, remains largely unexplored. We compared the dynamics of induced high gamma power (iHGP) across cortex in humans during speech-sound working memory in individuals with schizophrenia (SZ) and healthy comparison subjects (HC) using magnetoencephalography (MEG). SZ showed similar task performance to HC while utilizing different brain regions. During encoding of speech sounds, SZ lacked the correlation of iHGP with task performance in posterior superior temporal gyrus (STGp) that was observed in healthy subjects. Instead, SZ recruited the visual word form area (VWFA) during both stimulus encoding and response preparation. Importantly, VWFA activity during encoding correlated with the magnitude of SZ hallucinations, task performance and an independent measure of verbal working memory. These findings suggest that VWFA plasticity is harnessed to compensate for STGp dysfunction in schizophrenia patients with hallucinations.

Scientific reports (2020), Vol. 10, No. 1 (32483253) (3 citations)

Magnetoencephalography for Schizophrenia (2020)

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ABSTRACT Schizophrenia (Sz) is a chronic mental disorder characterized by disturbances in thought (such as delusions and confused thinking), perception (hearing voices), and behavior (lack of motivation). The lifetime prevalence of Sz is between 0.3% and 0.7%, with late adolescence and early adulthood, the peak period for the onset of psychotic symptoms. Causal factors in Sz include environmental and genetic factors and especially their interaction. About 50% of individuals with a diagnosis of Sz have lifelong impairment.

Keywords: Magnetoencephalography, Neuroimaging, Neuroradiologists, Schizophrenia

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336407) (3 citations)

Impaired theta phase coupling underlies frontotemporal dysconnectivity in schizophrenia (2020)

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ABSTRACT Frontotemporal dysconnectivity is a key pathology in schizophrenia. The specific nature of this dysconnectivity is unknown, but animal models imply dysfunctional theta phase coupling between hippocampus and medial prefrontal cortex (mPFC). We tested this hypothesis by examining neural dynamics in 18 participants with a schizophrenia diagnosis, both medicated and unmedicated; and 26 age, sex and IQ matched control subjects. All participants completed two tasks known to elicit hippocampal-prefrontal theta coupling: a spatial memory task (during magnetoencephalography) and a memory integration task. In addition, an overlapping group of 33 schizophrenia and 29 control subjects underwent PET to measure the availability of GABAARs expressing the α5 subunit (concentrated on hippocampal somatostatin interneurons). We demonstrate-in the spatial memory task, during memory recall-that theta power increases in left medial temporal lobe (mTL) are impaired in schizophrenia, as is theta phase coupling between mPFC and mTL. Importantly, the latter cannot be explained by theta power changes, head movement, antipsychotics, cannabis use, or IQ, and is not found in other frequency bands. Moreover, mPFC-mTL theta coupling correlated strongly with performance in controls, but not in subjects with schizophrenia, who were mildly impaired at the spatial memory task and no better than chance on the memory integration task. Finally, mTL regions showing reduced phase coupling in schizophrenia magnetoencephalography participants overlapped substantially with areas of diminished α5-GABAAR availability in the wider schizophrenia PET sample. These results indicate that mPFC-mTL dysconnectivity in schizophrenia is due to a loss of theta phase coupling, and imply α5-GABAARs (and the cells that express them) have a role in this process.

Keywords: hippocampus, prefrontal cortex, schizophrenia, spatial memory, theta

Brain: a journal of neurology (2020), Vol. 143, No. 4 (32236540) (27 citations)

Feature optimization method for machine learning-based diagnosis of schizophrenia using magnetoencephalography (2020)

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BACKGROUND When many features and a small number of clinical data exist, previous studies have used a few top-ranked features from the Fisher's discriminant ratio (FDR) for feature selection. However, there are many similarities between selected features. New method: To reduce the redundant features, we applied a technique employing FDR in conjunction with feature correlation. We performed an attention network test on schizophrenic patients and normal subjects with a 152-channel magnetoencephalograph. P300m amplitudes of event-related fields (ERFs) were used as features at the sensor level and P300m amplitudes of ERFs for 500 nodes on the cortex surface were used as features at the source level. Features were ranked using FDR criterion and cross-correlation measure, and then the highest ranked 10 features were selected and an exhaustive search was used to find combination having the maximum accuracy.

RESULTS At the sensor level, we found a single channel of the occipital region that distinguished the two groups with an accuracy of 89.7 %. At source level, we

obtained an accuracy of 96.2 % using two features, the left superior frontal region and the left inferior temporal region.

COMPARISON WITH EXISTING METHOD At source level, we obtained a higher accuracy than traditional method using only FDR criterion (accuracy = 88.5 %). We used only the P300 m amplitude (not latency) on a single channel and two brain regions at a fairly high rate.

Keywords: Diagnosis, Feature optimization, Machine learning, Magnetoencephalography, Schizophrenia

Journal of neuroscience methods (2020), Vol. 338 (32201352) (3 citations)

Localization of Early-Stage Visual Processing Deficits at Schizophrenia Spectrum Illness Onset Using Magnetoencephalography (2020)

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ABSTRACT Impairments in early-stage visual processing are observed in chronic psychosis. However, their presence, localization within the brain, and contribution to cognitive symptoms remain less well established early in disease course. The present study utilized magnetoencephalography (MEG) to examine sensory responses within primary visual cortex (V1). MEG was recorded from 38 individuals diagnosed with a schizophrenia spectrum illness at first psychotic episode (FESz) and 38 matched healthy controls (HC) during visual search tasks. The inverse solution for cortical activity contributing to the M100 visual evoked field was derived. Task performance and V1 activation were compared between groups. FESz exhibited a reduced V1 response relative to HC. This group deficit, however, was selective for the left hemisphere (LH). A similar interaction was observed for response time with FESz exhibiting slower responses to right visual field targets, a difference not observed among HC. Among FESz, larger LH V1 activity was associated with larger hallucination subscale scores on the Scale for the Assessment of Positive Symptoms. Early-stage visual processing deficits localized to V1 are present at disease onset in the schizophrenia spectrum. This impairment appears to be restricted to the LH, consistent with previous reports detailing a predominantly LH disease process in early psychosis, and activity within this region was associated with an increased experience of hallucinations. These findings detail the cortical responses contributing to visual processing impairments and their relationship with symptoms at disease onset, advancing our understanding of their developmental trajectory over the course of psychotic illness.

Keywords: first-break, lateralization, schizophrenia spectrum, sensory impairment

Schizophrenia bulletin (2020), Vol. 46, No. 4 (32052843) (9 citations)

Language-Related Neurophysiological Deficits in Schizophrenia (2020)

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ABSTRACT Schizophrenia is a severe psychiatric disorder that affects all aspects of one's life with several cognitive and social dysfunctions. However, there is still no objective and universal index for diagnosis and treatment of this disease. Many researchers have studied language processing in schizophrenia since most of the patients show symptoms related to language processing, such as thought disorder, auditory verbal hallucinations, or delusions. Electroencephalography (EEG) and magnetoencephalography (MEG) with millisecond order high temporal resolution, have been applied to reveal the abnormalities in language processing in

schizophrenia. The aims of this review are (a) to provide an overview of recent findings in language processing in schizophrenia with EEG and MEG using neurophysiological indices, providing insights into underlying language related pathophysiological deficits in this disease and (b) to emphasize the advantage of EEG and MEG in research on language processing in schizophrenia.

Keywords: electroencephalography (EEG), language processing, magnetoencephalography (MEG), neural oscillation, schizophrenia

Clinical EEG and neuroscience (2020), Vol. 51, No. 4 (31741393) (11 citations)

Reduced parietal alpha power and psychotic symptoms: Test-retest reliability of resting-state magnetoencephalography in schizophrenia and healthy controls (2020)

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BACKGROUND Despite increased reporting of resting-state magnetoencephalography (MEG), reliability of those measures remains scarce and predominately reported in healthy controls (HC). As such, there is limited knowledge on MEG resting-state reliability in schizophrenia (SZ).

METHODS To address test-retest reliability in psychosis, a reproducibility study of 26 participants (13-SZ, 13-HC) was performed. We collected eyes open and eyes closed resting-state data during 4 separate instances (2 Visits, 2 runs per visit) to estimate spectral power reliability (power, normalized power, alpha reactivity) across one hour and one week. Intraclass correlation coefficients (ICCs) were calculated. For source modeling, we applied an anatomically constrained linear estimation inverse model known as dynamic statistical parametric mapping (MNE dSPM) and source-based connectivity using the weighted phase lag index.

RESULTS Across one week there was excellent test-retest reliability in global spectral measures in theta-gamma bands (HC ICCAvg = 0.87, SZ ICCAvg = 0.87), regional spectral measures in all bands (HC ICCAvg = 0.86, SZ ICCAvg = 0.80), and parietal alpha measures (HC ICCAvg = 0.90, SZ ICCAvg = 0.84). Conversely, functional connectivity had poor reliability, as did source spectral power across one hour for SZ. Relative to HC, SZ also had reduced parietal alpha normalized power during eyes closed only, reduced alpha reactivity, and an association between higher PANSS positive scores and lower parietal alpha power.

CONCLUSIONS There was excellent to good test-retest reliability in most MEG spectral measures with a few exceptions in the schizophrenia patient group. Overall, these findings encourage the use of resting-state MEG while emphasizing the importance of determining reliability in clinical populations.

Keywords: MEG, Resting-state, Schizophrenia, Spectral power, Symptoms, Test-retest reliability

Schizophrenia research (2020), Vol. 215 (31706785) (10 citations)

Intervention-specific patterns of cortical function plasticity during auditory encoding in people with schizophrenia (2020)

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ABSTRACT Schizophrenia is a neurocognitive illness characterized by behavioral and neural impairments in both early auditory processing and higher order verbal working memory. Previously we have shown intervention-specific cognitive performance improvements with computerized, targeted training of auditory processing (AT) when compared to a computer games (CG) control intervention that emphasized visual processing. To investigate spatiotemporal changes in patterns of neural activity specific to the AT intervention, the current study used magnetoencephalography (MEG) imaging to derive induced high gamma band oscillations (HGO) during auditory encoding, before and after 50 h (10 weeks) of exposure to either the AT or CG intervention. During stimulus encoding, AT intervention-specific changes in high gamma activity occurred in left middle frontal and left middle-superior temporal cortices. In contrast, CG intervention-specific changes were observed in right medial frontal and supramarginal gyri during stimulus encoding, and in bilateral temporal cortices during response preparation. These data reveal that, in schizophrenia, intensive exposure to either training of auditory processing or exposure to visuospatial activities produces significant but complementary patterns of cortical function plasticity within a distributed fronto-temporal network. These results underscore the importance of delineating the specific neuroplastic effects of targeted behavioral interventions to ensure desired neurophysiological changes and avoid unintended consequences on neural system functioning.

Keywords: Cognitive training, Linguistic processing, Magnetoencephalography, Neuroplasticity

Schizophrenia research (2020), Vol. 215 (31648842) (6 citations)

Non-negative Matrix Factorization Reveals Resting-State Cortical Alpha Network Abnormalities in the First-Episode Schizophrenia Spectrum (2020)

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BACKGROUND Little is known about neural oscillatory dynamics in first-episode psychosis. Pathophysiology of functional connectivity can be measured through network activity of alpha oscillations, reflecting long-range communication between distal brain regions.

METHODS Resting magnetoencephalographic activity was collected from 31 individuals with first-episode schizophrenia spectrum psychosis and 22 healthy control individuals. Activity was projected to the realistic cortical surface, based on structural magnetic resonance imaging. The first principal component of activity in 40 Brodmann areas per hemisphere was Hilbert transformed within the alpha range. Non-negative matrix factorization was applied to single-trial alpha phase-locking values from all subjects to determine alpha networks. Within networks, energy and entropy were compared.

RESULTS Four cortical alpha networks were pathological in individuals with first-episode schizophrenia spectrum psychosis. The networks involved the bilateral anterior and posterior cingulate; left auditory, medial temporal, and cingulate cortex; right inferior frontal gyrus and widespread areas; and right posterior parietal cortex and widespread areas. Energy and entropy were associated with the Positive and Negative Syndrome Scale total and thought disorder factors for the first three networks. In addition, the left posterior temporal network was associated with positive and negative factors, and the right inferior frontal network was associated with the positive factor.

CONCLUSIONS Machine learning network analysis of resting alpha-band neural activity identified several aberrant networks in individuals with first-episode schizophrenia spectrum psychosis, including the left temporal, right inferior frontal, right posterior parietal, and bilateral cingulate cortices. Abnormal long-range alpha communication is evident at the first presentation for psychosis and may provide clues about mechanisms of dysconnectivity in psychosis and novel targets for noninvasive brain stimulation.

Keywords: Alpha, Machine learning, Magnetoencephalography, Network, Non-negative matrix factorization, Schizophrenia

Biological psychiatry. Cognitive neuroscience and neuroimaging (2020), Vol. 5, No. 10 (31451387) (10 citations)

Deficit Versus Nondeficit Schizophrenia: An MEG-EEG Investigation of Resting State and Source Coherence-Preliminary Data (2020)

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ABSTRACT This study investigated the magneto- and electroencephalography (MEG and EEG, respectively) resting state to identify the deviations closely associated with the deficit syndrome (DS) in schizophrenia patients. Ten subjects in each group (control, DS, and nondeficit schizophrenia [NDS]) were included. Subjects underwent MEG-EEG recordings during a resting state condition. MEG coherence source imaging (CSI) in source space and spectral analysis in sensor space were performed. Significant differences were found between the 2 patient groups: (1) MEG and EEG spectral analysis showed significantly higher power at low frequencies (delta band) at sensor space in DS compared with NDS patients; (2) source analysis revealed larger power in the DS compared with NDS group at low frequencies in the frontal region; (3) NDS patients showed significantly higher MEG signal relative power in beta bands in sensor space compared with DS patients; (4) both DS and NDS patients showed higher EEG absolute power at higher beta band compared to controls; and (5) patients with DS were found to have a significantly higher MEG CSI than controls in the beta frequency band. These data support the observation of increased power in the low-frequency EEG/MEG rhythms associated with the DS. Increased power in the beta rhythms was more associated with the NDS.

Keywords: EEG, MEG, coherence source imaging, deficit syndrome, electroencephalography, magnetoencephalography, resting state, schizophrenia

Clinical EEG and neuroscience (2020), Vol. 51, No. 1 (31379210) (5 citations)

Oscillatory, Computational, and Behavioral Evidence for Impaired GABAergic Inhibition in Schizophrenia (2020)

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ABSTRACT The dysconnection hypothesis of schizophrenia (SZ) proposes that psychosis is best understood in terms of aberrant connectivity. Specifically, it suggests that dysconnectivity arises through aberrant synaptic modulation associated with deficits in GABAergic inhibition, excitation-inhibition balance and disturbances of high-frequency oscillations. Using a computational model combined with a graded-difficulty visual orientation discrimination paradigm, we demonstrate that, in SZ, perceptual performance is determined by the balance of excitation-inhibition in superficial cortical layers. Twenty-eight individuals with a DSM-IV diagnosis of SZ, and 30 age- and gender-matched healthy controls participated in a psychophysics orientation discrimination task, a visual grating magnetoencephalography (MEG) recording, and a magnetic resonance spectroscopy (MRS) scan for GABA. Using a neurophysiologically informed model, we quantified group differences in GABA, gamma measures, and the predictive validity of model parameters for orientation discrimination in the SZ group. MEG visual gamma frequency was reduced in SZ, with lower peak frequency associated with more severe negative symptoms. Orientation discrimination performance was impaired in SZ. Dynamic causal modeling of the MEG data showed that local synaptic connections were reduced in SZ and local inhibition correlated negatively with the severity of negative symptoms. The effective connectivity between inhibitory interneurons and superficial pyramidal cells predicted orientation discrimination performance within the SZ group; consistent with graded, behaviorally relevant, disease-related changes in local GABAergic connections. Occipital GABA levels were significantly reduced in SZ but did not predict behavioral performance or oscillatory measures. These findings endorse the importance, and behavioral relevance, of GABAergic synaptic disconnection in schizophrenia that underwrites excitation-inhibition balance.

Keywords: GABA, behavioral, dysconnection, inhibition, oscillatory, schizophrenia

Schizophrenia bulletin (2020), Vol. 46, No. 2 (31219602) (24 citations)

Stroke

Time course of right-hemisphere recruitment during word production following left-hemisphere damage: A single case of young stroke (2022)

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ABSTRACT Our understanding of post-stroke language function is largely based on older age groups, who show increasing age-related brain pathology and neural reorganisation. To illustrate language outcomes in the young-adult brain, we present the case of J., a 23-year-old woman with chronic aphasia from a left-hemisphere stroke affecting the temporal lobe. Diffusion MRI-based tractography indicated that J.'s language-relevant white-matter structures were severely damaged. Employing magnetoencephalography (MEG), we explored J.'s conceptual preparation and word planning abilities using context-driven and bare picture-naming tasks. These revealed naming deficits, manifesting as word-finding difficulties and semantic paraphasias about half of the time. Naming was however facilitated by semantically constraining lead-in sentences. Altogether, this pattern indicates disrupted lexical-semantic and phonological retrieval abilities. MEG revealed that J.'s conceptual and naming-related neural responses were supported by the right hemisphere, compared to the typical left-lateralised brain response of a matched control. Differential recruitment of right-hemisphere structures (330-440 ms post-picture onset) was found concurrently during successful naming (right mid-to-posterior temporal lobe) and word-finding attempts (right inferior frontal gyrus). Disconnection of the temporal lobes via corpus callosum was not critical for recruitment of the right hemisphere in visually guided naming, possibly due to neural activity right lateralising from the outset. Although J.'s right hemisphere responded in a timely manner during word planning, its lexical and phonological retrieval abilities remained modest.

Keywords: alpha oscillations, beta oscillations, event-related fields, language lateralisation, splenium

The European journal of neuroscience (2022), Vol. 56, No. 8 (36028218) (1 citation)

Electrophysiological connectivity markers of preserved language functions in post-stroke aphasia (2022)

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ABSTRACT Post-stroke aphasia is a consequence of localized stroke-related damage as well as global disturbances in a highly interactive and bilaterally-distributed language network. Aphasia is increasingly accepted as a network disorder and it should be treated as such when examining the reorganization and recovery mechanisms after stroke. In the current study, we sought to investigate reorganized patterns of electrophysiological connectivity, derived from resting-state magnetoencephalography (rsMEG), in post-stroke chronic (>6 months after onset) aphasia. We implemented amplitude envelope correlations (AEC), a metric of connectivity commonly used to describe slower aspects of interregional communication in resting-state electrophysiological data. The main focus was on identifying the oscillatory frequency bands and frequency-specific spatial topology of connections associated with preserved language abilities after stroke. RsMEG was recorded for 5 min in 21 chronic stroke survivors with aphasia and in 20 matched healthy controls. Source-level MEG activity was reconstructed and summarized within 72 atlas-defined brain regions (or nodes). A 72 × 72 leakage-corrected connectivity (of AEC) matrix was obtained for frequencies from theta to low-gamma (4-50 Hz). Connectivity was compared between groups, and, the correlations between connectivity and subscale scores from the Western Aphasia Battery (WAB) were evaluated in the stroke group, using partial least squares analyses. Posthoc multiple regression analyses were also conducted on a graph theory measure of node strengths, derived from significant connectivity results, to control for node-wise properties (local spectral power and lesion sizes) and demographic and stroke-related variables. Connectivity among the left hemisphere regions, i.e. those ipsilateral to the stroke lesion, was greatly reduced in stroke survivors with aphasia compared to matched healthy controls in the alpha (8-13 Hz; $p = 0.011$) and beta (15-30 Hz; $p = 0.001$) bands. The spatial topology of hypoconnectivity in the alpha vs. beta bands was distinct, revealing a greater involvement of ventral frontal, temporal and parietal areas in alpha, and dorsal frontal and parietal areas in beta. The node strengths from alpha and beta group differences remained significant after controlling for nodal spectral power. AEC correlations with WAB subscales of object naming and fluency were significant. Greater alpha connectivity was associated with better naming performance ($p = 0.045$), and greater connectivity in both the alpha ($p = 0.033$) and beta ($p = 0.007$) bands was associated with better speech fluency performance. The spatial topology was distinct between these frequency bands. The node strengths remained significant after controlling for age, time post stroke onset, nodal spectral power and nodal lesion sizes. Our findings provide important insights into the electrophysiological connectivity profiles (frequency and spatial topology) potentially underpinning preserved language abilities in stroke survivors with aphasia.

Keywords: Amplitude envelope correlations, Aphasia, Functional connectivity, Magnetoencephalography (MEG), Resting-state, Stroke

NeuroImage. Clinical (2022), Vol. 34 (35561556) (1 citation)

Functional connectivity drives stroke recovery: shifting the paradigm from correlation to causation (2022)

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ABSTRACT Stroke is a leading cause of disability, with deficits encompassing multiple functional domains. The heterogeneity underlying stroke poses significant challenges in the prediction of post-stroke recovery, prompting the development of neuroimaging-based biomarkers. Structural neuroimaging measurements, particularly those reflecting corticospinal tract injury, are well-documented in the literature as potential

biomarker candidates of post-stroke motor recovery. Consistent with the view of stroke as a 'circuitopathy', functional neuroimaging measures probing functional connectivity may also prove informative in post-stroke recovery. An important step in the development of biomarkers based on functional neural network connectivity is the establishment of causality between connectivity and post-stroke recovery. Current evidence predominantly involves statistical correlations between connectivity measures and post-stroke behavioural status, either cross-sectionally or serially over time. However, the advancement of functional connectivity application in stroke depends on devising experiments that infer causality. In 1965, Sir Austin Bradford Hill introduced nine viewpoints to consider when determining the causality of an association: (i) strength; (ii) consistency; (iii) specificity; (iv) temporality; (v) biological gradient; (vi) plausibility; (vii) coherence; (viii) experiment; and (ix) analogy. Collectively referred to as the Bradford Hill Criteria, these points have been widely adopted in epidemiology. In this review, we assert the value of implementing Bradford Hill's framework to stroke rehabilitation and neuroimaging. We focus on the role of neural network connectivity measurements acquired from task-oriented and resting-state functional MRI, EEG, magnetoencephalography and functional near-infrared spectroscopy in describing and predicting post-stroke behavioural status and recovery. We also identify research opportunities within each Bradford Hill tenet to shift the experimental paradigm from correlation to causation.

Keywords: causality, connectivity, neuroimaging, rehabilitation, stroke

Brain: a journal of neurology (2022), Vol. 145, No. 4 (34932786) (7 citations)

CMC is more than a measure of corticospinal tract integrity in acute stroke patients (2021)

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ABSTRACT In healthy subjects, motor cortex activity and electromyographic (EMG) signals from contracting contralateral muscle show coherence in the beta (15-30 Hz) range. Corticomuscular coherence (CMC) is considered a sign of functional coupling between muscle and brain. Based on prior studies, CMC is altered in stroke, but functional significance of this finding has remained unclear. Here, we examined CMC in acute stroke patients and correlated the results with clinical outcome measures and corticospinal tract (CST) integrity estimated with diffusion tensor imaging (DTI). During isometric contraction of the extensor carpi radialis muscle, EMG and magnetoencephalographic oscillatory signals were recorded from 29 patients with paresis of the upper extremity due to ischemic stroke and 22 control subjects. CMC amplitudes and peak frequencies at 13-30 Hz were compared between the two groups. In the patients, the peak frequency in both the affected and the unaffected hemisphere was significantly ($p < 0.01$) lower and the strength of CMC was significantly ($p < 0.05$) weaker in the affected hemisphere compared to the control subjects. The strength of CMC in the patients correlated with the level of tactile sensitivity and clinical test results of hand function. In contrast, no correlation between measures of CST integrity and CMC was found. The results confirm the

earlier findings that CMC is altered in acute stroke and demonstrate that CMC is bidirectional and not solely a measure of integrity of the efferent corticospinal tract.

Keywords: Afferent input, Corticomuscular coherence, Corticospinal tract integrity, Magnetoencephalography, Motor cortex, Stroke

NeuroImage. Clinical (2021), Vol. 32 (34555801) (0 citations)

Poststroke acute dysexecutive syndrome, a disorder resulting from minor stroke due to disruption of network dynamics (2020)

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ABSTRACT Stroke patients with small central nervous system infarcts often demonstrate an acute dysexecutive syndrome characterized by difficulty with attention, concentration, and processing speed, independent of lesion size or location. We use magnetoencephalography (MEG) to show that disruption of network dynamics may be responsible. Nine patients with recent minor strokes and eight age-similar controls underwent cognitive screening using the Montreal cognitive assessment (MoCA) and MEG to evaluate differences in cerebral activation patterns. During MEG, subjects participated in a visual picture-word matching task. Task complexity was increased as testing progressed. Cluster-based permutation tests determined differences in activation patterns within the visual cortex, fusiform gyrus, and lateral temporal lobe. At visit 1, MoCA scores were significantly lower for patients than controls (median [interquartile range] = 26.0 [4] versus 29.5 [3], P = 0.005), and patient reaction times were increased. The amplitude of activation was significantly lower after infarct and demonstrated a pattern of temporal dispersion independent of stroke location. Differences were prominent in the fusiform gyrus and lateral temporal lobe. The pattern suggests that distributed network dysfunction may be responsible. Additionally, controls were able to modulate their cerebral activity based on task difficulty. In contrast, stroke patients exhibited the same low-amplitude response to all stimuli. Group differences remained, to a lesser degree, 6 mo later; while MoCA scores and reaction times improved for patients. This study suggests that function is a globally distributed property beyond area-specific functionality and illustrates the need for longer-term follow-up studies to determine whether abnormal activation patterns ultimately resolve or another mechanism underlies continued recovery.

Keywords: magnetoencephalography, recovery, stroke

Proceedings of the National Academy of Sciences of the United States of America (2020), Vol. 117, No. 52 (33318200) (5 citations)

High definition transcranial direct current stimulation modulates abnormal neurophysiological activity in post-stroke aphasia (2020)

Shah-Basak, Priyanka P; Sivaratnam, Gayatri; Teti, Selina; Francois-Nienaber, Alexander; Yossofzai, Maryam; Armstrong, Sabrina; Nayar, Sumiti; Jokel, Regina; Meltzer, Jed

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ABSTRACT Recent findings indicate that measures derived from resting-state magnetoencephalography (rs-MEG) are sensitive to cortical dysfunction in post-stroke aphasia. Spectral power and multiscale entropy (MSE) measures show that left-hemispheric areas surrounding the stroke lesion (perilesional) exhibit pathological oscillatory slowing and alterations in signal complexity. In the current study, we tested whether individually-targeted high-definition transcranial direct current stimulation (HD-tDCS) can reduce MEG abnormalities and transiently improve language performance. In eleven chronic aphasia survivors, we devised a method to localize perilesional areas exhibiting peak MSE abnormalities, and subsequently targeted these areas with excitatory/anodal-tDCS, or targeted the contralateral homolog areas with inhibitory/cathodal-tDCS, based on prominent theories of stroke recovery. Pathological MEG slowing in these patients was correlated with aphasia severity. Sentence/phrase repetition accuracy was assessed before and after tDCS. A delayed word reading task was administered inside MEG to assess tDCS-induced neurophysiological changes in relative power and MSE computed on the pre-stimulus and delay task time windows. Results indicated increases in repetition accuracy, decreases in contralateral theta (4-7 Hz) and coarse-scale MSE (slow activity), and increases in perilesional low-gamma (25-50 Hz) and fine-scale MSE (fast activity) after anodal-tDCS, indicating reversal of pathological abnormalities. RsMEG may be a sensitive measure for guiding therapeutic tDCS.

Scientific reports (2020), Vol. 10, No. 1 (33184382) (6 citations)

Cortical neural activity evoked by bilateral and unilateral mirror therapy after stroke (2020)

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OBJECTIVE This study aimed to investigate the differential effects of bilateral and unilateral mirror therapy (MT) on motor cortical activations in stroke patients by magnetoencephalography (MEG).

METHODS Sixteen stroke patients and 16 right-handed healthy volunteers were recruited. All participants were required to perform 4 conditions: resting, no mirror with bilateral hand movements (Bilateral-No mirror), mirror with bilateral hand movements (Bilateral-Mirror) and mirror with unilateral hand movements (Unilateral-Mirror). Beta oscillatory activities in the primary motor cortex (M1) were collected during each condition using MEG. The percentage change of beta oscillatory activity was calculated for each condition to correct the baseline differences.

RESULTS In the stroke group, the percentage change of M1 beta oscillatory activity significantly decreased more in the Bilateral-Mirror condition than in the Bilateral-No mirror and Unilateral-Mirror conditions. In the healthy group, no significant differences in the percentage change of beta oscillatory activity were found among the 3 conditions. Further, a significant difference in the percentage change of beta oscillatory activity only in the Bilateral-Mirror condition was found between the 2 groups.

CONCLUSIONS This study provides new information on the differential cortical activations modulated by bilateral and unilateral MT.

SIGNIFICANCE Bilateral MT led to greater M1 neural activities than unilateral MT and bilateral movements without a mirror in stroke patients.

Keywords: Mirror therapy, Mirror visual feedback, Stroke, magnetoencephalography (MEG)

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 10 (32828035) (6 citations)

Neurophysiological signatures of hand motor response to dual-transcranial direct current stimulation in subacute stroke: a TMS and MEG study (2020)

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BACKGROUND Dual transcranial direct current stimulation (tDCS) to the bilateral primary motor cortices (M1s) has potential benefits in chronic stroke, but its effects in subacute stroke, when behavioural effects might be expected to be greater, have been relatively unexplored. Here, we examined the neurophysiological effects and the factors influencing responsiveness of dual-tDCS in subacute stroke survivors.

METHODS We conducted a randomized sham-controlled crossover study in 18 survivors with first-ever, unilateral subcortical ischaemic stroke 2-4 weeks after stroke onset and 14 matched healthy controls. Participants had real dual-tDCS (with an ipsilesional [right for controls] M1 anode and a contralesional M1 [left for controls] cathode; 2 mA for 20mins) and sham dual-tDCS on separate days, with concurrent paretic [left for controls] hand exercise. Using transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG), we recorded motor evoked potentials (MEPs), the ipsilateral silent period (iSP), short-interval intracortical inhibition, and finger movement-related cortical oscillations before and immediately after tDCS.

RESULTS Stroke survivors had decreased excitability in ipsilesional M1 with a relatively excessive transcallosal inhibition from the contralesional to ipsilesional hemisphere at baseline compared with controls, as quantified by decreased MEPs and increased iSP duration. Dual-tDCS led to increased MEPs and decreased iSP duration in ipsilesional M1. The magnitude of the tDCS-induced MEP increase in stroke survivors was predicted by baseline contralesional-to-ipsilesional transcallosal inhibition (iSP) ratio. Baseline post-movement synchronization in α-band activity in ipsilesional M1 was decreased after stroke compared with controls, and its tDCS-induced increase correlated with upper limb score in stroke survivors. No significant adverse effects were observed during or after dual-tDCS.

CONCLUSIONS Task-concurrent dual-tDCS in subacute stroke can safely and effectively modulate bilateral M1 excitability and inter-hemispheric imbalance and also movement-related α-activity.

Keywords: Magnetoencephalography, Plasticity, Subacute stroke, Transcallosal inhibition, Transcranial direct current stimulation, Transcranial magnetic stimulation

Journal of neuroengineering and rehabilitation (2020), Vol. 17, No. 1 (32527268) (9 citations)

The sensitivity of event-related potentials/fields to logopedic interventions in patients with stroke-related aphasia (2020)

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ABSTRACT Recovery of stroke-related aphasia can be affected by language therapy in the early and chronic stage. Objectively monitoring therapy-induced neuroplasticity is possible by several measurement techniques including electro- and magneto-encephalography. The obtained event-related potentials (ERPs) and fields (ERFs) provide insights into the neural basis of intact or deficient language processing with milliseconds precision. In this literature review, we highlight the sensitivity of ERPs and ERFs to logopedic interventions by providing an overview of therapy-induced changes in the amplitude, latency and topography of early and mid-to-late components.

Keywords: Aphasia, Event-related fields, Event-related potentials, Language therapy, Neuroplasticity, Stroke

Acta neurologica Belgica (2020), Vol. 120, No. 4 (32474880) (5 citations)

β-Oscillations Reflect Recovery of the Paretic Upper Limb in Subacute Stroke (2020)

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ABSTRACT Background. Recovery of upper limb function post-stroke can be partly predicted by initial motor function, but the mechanisms underpinning these improvements have yet to be determined. Here, we sought to identify neural correlates of post-stroke recovery using longitudinal magnetoencephalography (MEG) assessments in subacute stroke survivors. Methods. First-ever, subcortical ischemic stroke survivors with unilateral mild to moderate hand paresis were evaluated at 3, 5, and 12 weeks after stroke using a finger-lifting task in the MEG. Cortical activity patterns in the β-band (16-30 Hz) were compared with matched healthy controls. Results. All stroke survivors (n=22; 17 males) had improvements in action research arm test (ARAT) and Fugl-Meyer upper extremity (FM-UE) scores between 3 and 12 weeks. At 3 weeks post-stroke the peak amplitudes of the movement-related ipsilesional β-band event-related desynchronization (β-ERD) and synchronization (β-ERS) in primary motor cortex (M1) were significantly lower than the healthy controls (p<0.001) and were correlated with both the FM-UE and ARAT scores (r=0.51-0.69, p<0.017). The decreased β-ERS peak amplitudes were observed both in paretic and non-paretic hand movement particularly at 3 weeks post-stroke, suggesting a generalized disinhibition status. The peak amplitudes of ipsilesional β-ERS at week 3 post-stroke correlated with the FM-UE score at 12 weeks (r=0.54, p=0.03) but no longer significant when controlling for the FM-UE score at 3 weeks post-stroke.Conclusions. Although early β-band activity does not independently predict outcome at 3 months after stroke, it mirrors functional changes, giving a potential

insight into the mechanisms underpinning recovery of motor function in subacute stroke.

Keywords: event-related desynchronization, event-related synchronization, magnetoencephalography, motor recovery, stroke, β-oscillations

Neurorehabilitation and neural repair (2020), Vol. 34, No. 5 (32321366) (12 citations)

Central auditory processing in adults with chronic stroke without hearing loss: A magnetoencephalography study (2020)

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OBJECTIVE Stroke lesions in non-auditory areas may affect higher-order central auditory processing. We sought to characterize auditory functions in chronic stroke survivors with unilateral arm/hand impairment using auditory evoked responses (AERs) with lesion and perception metrics.

METHODS The AERs in 29 stroke survivors and 14 controls were recorded with single tones, active and passive frequency-oddballs, and a dual-oddball with pitch-contour and time-interval deviants. Performance in speech-in-noise, mistuning detection, and moving-sound detection was assessed. Relationships between AERs, behaviour, and lesion overlap with functional networks, were examined.

RESULTS Despite their normal hearing, eight patients showed unilateral AER in the hemisphere ipsilateral to the affected hand with reduced amplitude compared to those with bilateral AERs. Both groups showed increasing attenuation of later components. Hemispheric asymmetry of AER sources was reduced in bilateral-AER patients. The N1 wave (100 ms latency) and P2 (200 ms) were delayed in individuals with lesions in the basal-ganglia and white-matter, while lesions in the attention network reduced the frequency-MMN (mismatch negativity) responses and increased the pitch-contour P3a response. Patients' impaired speech-in-noise perception was explained by AER measures and frequency-deviant detection performance with multiple regression.

CONCLUSION AERs reflect disruption of auditory functions due to damage outside of temporal lobe, and further explain complexity of neural mechanisms underlying higher-order auditory perception.

SIGNIFICANCE Stroke survivors without obvious hearing problems may benefit from rehabilitation for central auditory processing.

Keywords: Auditory evoked responses, Central auditory processing, Chronic stroke, Hearing, Magnetoencephalography, Mismatch negativity

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2020), Vol. 131, No. 5 (32200092) (0 citations)

Traumatic Brain Injury

MEG measured delta waves increase in adolescents after concussion (2022)

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INTRODUCTION The purpose of this study is to determine if delta waves, measured by magnetoencephalography (MEG), increase in adolescents due to a sports concussion.

METHODS Twenty-four adolescents (age 14-17) completed pre- and postseason MRI and MEG scanning. MEG whole-brain delta power was calculated for each subject and normalized by the subject's total power. In eight high school football players diagnosed with a concussion during the season (mean age = 15.8), preseason delta power was subtracted from their postseason scan. In eight high school football players without a concussion (mean age = 15.7), preseason delta power was subtracted from postseason delta power and in eight age-matched noncontact controls (mean age = 15.9), baseline delta power was subtracted from a 4-month follow-up scan. ANOVA was used to compare the mean differences between preseason and postseason scans for the three groups of players, with pairwise comparisons based on Student's t-test method.

RESULTS Players with concussions had significantly increased delta wave power at their postseason scans than nonconcussed players ($p = .018$) and controls ($p = .027$).

CONCLUSION We demonstrate that a single concussion during the season in adolescent subjects can increase MEG measured delta frequency power at their postseason scan. This adds to the growing body of literature indicating increased delta power following a concussion.

Keywords: concussion, delta waves, football, magnetoencephalography (MEG)

Brain and behavior (2022), Vol. 12, No. 9 (36053126) (1 citation)

Memory retrieval brain-behavior disconnection in mild traumatic brain injury: A magnetoencephalography and diffusion tensor imaging study (2022)

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ABSTRACT Mild traumatic brain (mTBI) injury is often associated with long-term cognitive and behavioral complications, including an increased risk of memory impairment. Current research challenges include a lack of cross-modal convergence regarding the underlying neural-behavioral mechanisms of mTBI, which hinders therapeutics and outcome management for this frequently under-treated and vulnerable population. We used multi-modality imaging methods including magnetoencephalography (MEG) and diffusion tensor imaging (DTI) to investigate brain-behavior impairment in mTBI related to working memory. A total of 41 participants were recruited, including 23 patients with a first-time mTBI imaged within 3 months of injury (all male, age = 29.9, SD = 6.9), and 18 control participants (all male, age = 27.3, SD = 5.3). Whole-brain statistics revealed spatially concomitant functional-structural disruptions in brain-behavior interactions in working memory in the mTBI group compared with the control group. These disruptions are located in the hippocampal-prefrontal region and, additionally, in the amygdala (measured by MEG neural activation and DTI measures of fractional anisotropy in relation to working memory performance; $p < .05$, two-way ANCOVA, nonparametric permutations, corrected). Impaired brain-behavior connections found in the hippocampal-prefrontal and amygdala circuits indicate brain dysregulation of memory, which may leave mTBI patients vulnerable to increased environmental demands exerting memory resources, leading to related cognitive and emotional psychopathologies. The findings yield clinical implications and highlight a need for early rehabilitation after mTBI, including attention- and sensory-based behavioral exercises.

Keywords: diffusion tensor imaging, hippocampus, magnetoencephalography, mild traumatic brain injury, working memory

Human brain mapping (2022), Vol. 43, No. 17 (35796166) (1 citation)

Mild traumatic brain injury impairs the coordination of intrinsic and motor-related neural dynamics (2021)

Rier, Lukas; Zamyadi, Rouzbeh; Zhang, Jing; Emami, Zahra; Seedat, Zelekha A; Mocanu, Sergiu; Gascoyne, Lauren E; Allen, Christopher M; Scadding, John W; Furlong, Paul L; Gooding-Williams, Gerard; Woolrich, Mark W; Evangelou, Nikos; Brookes, Matthew J; Dunkley, Benjamin T

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ABSTRACT Mild traumatic brain injury (mTBI) poses a considerable burden on healthcare systems. Whilst most patients recover quickly, a significant number suffer from sequelae that are not accompanied by measurable structural damage. Understanding the neural underpinnings of these debilitating effects and developing a means to detect injury, would address an important unmet clinical need. It could inform interventions and help predict prognosis. Magnetoencephalography (MEG) affords excellent sensitivity in probing neural function and presents significant promise for assessing mTBI, with abnormal neural oscillations being a potential specific biomarker. However, growing evidence suggests that neural dynamics are (at least in part) driven by transient, pan-spectral bursting and in

this paper, we employ this model to investigate mTBI. We applied a Hidden Markov Model to MEG data recorded during resting state and a motor task and show that previous findings of diminished intrinsic beta amplitude in individuals with mTBI are largely due to the reduced beta band spectral content of bursts, and that diminished beta connectivity results from a loss in the temporal coincidence of burst states. In a motor task, mTBI results in diminished burst amplitude, altered modulation of burst probability during movement, and a loss in connectivity in motor networks. These results suggest that, mechanistically, mTBI disrupts the structural framework underlying neural synchrony, which impairs network function. Whilst the damage may be too subtle for structural imaging to see, the functional consequences are detectable and persist after injury. Our work shows that mTBI impairs the dynamic coordination of neural network activity and proposes a potent new method for understanding mTBI.

Keywords: Beta bursts, Concussion, MEG, Networks, mTBI, mild Traumatic Brain Injury

NeuroImage. Clinical (2021), Vol. 32 (34653838) (1 citation)

Neuroimaging Correlates of Syndromal Anxiety Following Traumatic Brain Injury: A Systematic Review of the Literature (2022)

Jahed, Sahar; Daneshvari, Nicholas O; Liang, Angela L; Richey, Lisa N; Bryant, Barry R; Krieg, Akshay; Bray, Michael J C; Pradeep, Tejus; Luna, Licia P; Trapp, Nicholas T; Jones, Melissa B; Stevens, Daniel A; Roper, Carrie; Goldwaser, Eric L; Berich-Anastasio, Emily; Pletnikova, Alexandra; Lobner, Katie; Lee, Daniel J; Lauterbach, Margo; Sair, Haris I; Peters, Matthew E

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BACKGROUND Traumatic brain injury (TBI) can precipitate new-onset psychiatric symptoms or worsen existing psychiatric conditions. To elucidate specific mechanisms for this interaction, neuroimaging is often used to study both psychiatric conditions and TBI. This systematic review aims to synthesize the existing literature of neuroimaging findings among patients with anxiety after TBI.

METHODS We conducted a Preferred Reporting Items for Systematic Review and Meta-Analyses-compliant literature search via PubMed (MEDLINE), PsychINFO, EMBASE, and Scopus databases before May, 2019. We included studies that clearly defined TBI, measured syndromal anxiety as a primary outcome, and statistically analyzed the relationship between neuroimaging findings and anxiety symptoms.

RESULTS A total of 5982 articles were retrieved from the systematic search, of which 65 studied anxiety and 13 met eligibility criteria. These studies were published between 2004 and 2017, collectively analyzing 764 participants comprised of 470 patients with TBI and 294 non-TBI controls. Imaging modalities used included magnetic resonance imaging, functional magnetic resonance imaging, diffusion tensor imaging, electroencephalogram, magnetic resonance spectrometry, and magnetoencephalography. Eight of 13 studies presented at least one significant finding and together reflect a complex set of changes that lead to anxiety in the setting of TBI. The left cingulate gyrus in particular was found to be significant in 2 studies using different imaging modalities. Two studies also revealed perturbances in functional connectivity within the default mode network.

CONCLUSIONS This is the first systemic review of neuroimaging changes associated with anxiety after TBI, which implicated multiple brain structures and circuits, such as the default mode network. Future research with consistent, rigorous measurements of TBI and syndromal anxiety, as well as attention to control groups, previous TBIs, and time interval between TBI and neuroimaging, are warranted. By understanding neuroimaging correlates of psychiatric symptoms, this work could inform future post-TBI screening and surveillance, preventative efforts, and early interventions to improve neuropsychiatric outcomes.

Keywords: anxiety, neuroimaging, neuropsychiatric symptoms, traumatic brain injury

Journal of the Academy of Consultation-Liaison Psychiatry (2022), Vol. 63, No. 2 (34534701) (1 citation)

Alterations in the Magnetoencephalography Default Mode Effective Connectivity following Concussion (2021)

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BACKGROUND AND PURPOSE Magnetoencephalography is sensitive to functional connectivity changes associated with concussion. However, the directional influences between functionally related regions remain unexplored. In this study, we therefore evaluated concussion-related magnetoencephalography-based effective connectivity changes within resting-state default mode network regions.

MATERIALS AND METHODS Resting-state magnetoencephalography was acquired for 8 high school football players with concussion at 3 time points (preseason, postconcussion, postseason), as well as 8 high school football players without concussion and 8 age-matched controls at 2 time points (preseason, postseason). Time-series from the default mode network regions were extracted, and effective connectivity between them was computed for 5 different frequency bands. The default mode network regions were grouped into anterior and posterior default mode networks. The combined posterior-to-anterior and anterior-to-posterior effective connectivity values were averaged to generate 2 sets of values for each subject. The effective connectivity values were compared using a repeated measures ANOVA across time points for the concussed, nonconcussed, and control groups, separately.

RESULTS A significant increase in posterior-to-anterior effective connectivity from preseason to postconcussion (corrected P value = .013) and a significant decrease in posterior-to-anterior effective connectivity from postconcussion to postseason (corrected P value = .028) were observed in the concussed group. Changes in effective connectivity were only significant within the delta band. Anterior-to-posterior connectivity demonstrated no significant change. Effective connectivity in the nonconcussed group and controls did not show significant differences.

CONCLUSIONS The unidirectional increase in effective connectivity postconcussion may elucidate compensatory processes, invoking use of posterior regions to aid the function of susceptible anterior regions following brain injury. These findings support the potential value of magnetoencephalography in exploring directional changes of the brain network following concussion.

AJNR. American journal of neuroradiology (2021), Vol. 42, No. 10 (34503943) (1 citation)

Alterations in the Topology of Functional Connectomes Are Associated with Post-Traumatic Stress Disorder and Blast-Related Mild Traumatic Brain Injury in Combat Veterans (2021)

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ABSTRACT Post-traumatic stress disorder (PTSD) is a common condition in post-deployment service members (SM). SMs of the conflicts in Iraq and Afghanistan also frequently experience traumatic brain injury (TBI) and exposure to blasts during deployments. This study evaluated the effect of these conditions and experiences on functional brain connectomes in post-deployment, combat-exposed veterans. Functional brain connectomes were created using 5-min resting-state magnetoencephalography data. Well-established clinical interviews determined current PTSD diagnosis, as well as deployment-acquired mild TBI and history of exposure to blast. Linear regression examined the effect of these conditions on functional brain connectomes beyond covariates. There were significant interactions between blast-related mild TBI and PTSD after correction for multiple comparisons including number of nodes (non-standardized parameter estimate [PE] = -12.47), average degree (PE = 0.05), and connection strength (PE = 0.05). A main effect of blast-related mild TBI was observed on the threshold level. These results demonstrate a distinct functional connectome presentation associated with the presence of both blast-related mild TBI and PTSD. These findings suggest the possibility that blast-related mild TBI alterations in functional brain connectomes affect the presentation or progression of recovery from PTSD. The current results offer mixed support for hyper-connectivity in the chronic phase of deployment TBI.

Keywords: PTSD, TBI, connectome, deployment, network

Journal of neurotrauma (2021), Vol. 38, No. 22 (34435885) (4 citations)

Teasing apart trauma: neural oscillations differentiate individual cases of mild traumatic brain injury from post-traumatic stress disorder even when symptoms overlap (2021)

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ABSTRACT Post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are highly prevalent and closely related disorders. Affected individuals often exhibit substantially overlapping symptomatology - a major challenge for differential diagnosis in both military and civilian contexts. According to our symptom assessment, the PTSD group exhibited comparable levels of concussion symptoms and severity to the mTBI group. An objective and reliable system to uncover the key neural signatures differentiating these disorders would be an important step towards translational and applied clinical use. Here we explore use of MEG (magnetoencephalography)-multivariate statistical learning analysis in identifying the neural features for differential PTSD/mTBI characterisation. Resting state MEG-derived regional neural activity and coherence (or functional connectivity) across seven canonical neural oscillation frequencies (delta to high gamma) were used. The selected features were consistent and largely confirmatory with previously established neurophysiological markers for the two disorders. For regional power from theta, alpha and high gamma bands, the amygdala, hippocampus and temporal areas were identified. In line with regional activity, additional connections within the occipital, parietal and temporal regions were selected across a number of frequency bands. This study is the first to employ MEG-derived neural features to reliably and differentially stratify the two disorders

in a multi-group context. The features from alpha and beta bands exhibited the best classification performance, even in cases where distinction by concussion symptom profiles alone were extremely difficult. We demonstrate the potential of using 'invisible' neural indices of brain functioning to understand and differentiate these debilitating conditions.

Translational psychiatry (2021), Vol. 11, No. 1 (34088901) (2 citations)

Magnetoencephalography abnormalities in adult mild traumatic brain injury: A systematic review (2021)

Allen, Christopher M; Halsey, Lloyd; Topcu, Gogem; Rier, Lukas; Gascoyne, Lauren E; Scadding, John W; Furlong, Paul L; Dunkley, Benjamin T; das Nair, Roshan; Brookes, Matthew J; Evangelou, Nikos

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BACKGROUND The global incidence of traumatic brain injuries is rising, with at least 80% being classified as mild. These mild injuries are not visible on routine clinical imaging. The potential clinical role of a specific imaging biomarker be it diagnostic, prognostic or directing and monitoring progress of personalised treatment and rehabilitation has driven the exploration of several new neuroimaging modalities. This systematic review examined the evidence for magnetoencephalography (MEG) to provide an imaging biomarker in mild traumatic brain injury (mTBI).

METHODS Our review was prospectively registered on PROSPERO: CRD42019151387. We searched EMBASE, MEDLINE, trial registers, PsycINFO, Cochrane Library and conference abstracts and identified 37 papers describing MEG changes in mTBI eligible for inclusion. Since meta-analysis was not possible, based on the heterogeneity of reported outcomes, we provide a narrative synthesis of results.

RESULTS The two most promising MEG biomarkers are excess resting state low frequency power, and widespread connectivity changes in all frequency bands. These may represent biomarkers with potential for diagnostic application, which reflect time sensitive changes, or may be capable of offering clinically relevant prognostic information. In addition, the rich data that MEG produces are well-suited to new methods of machine learning analysis, which is now being actively explored.

INTERPRETATION MEG reveals several promising biomarkers, in the absence of structural abnormalities demonstrable with either computerised tomography or magnetic resonance imaging. This review has not identified sufficient evidence to support routine clinical use of MEG in mTBI currently. However, verifying MEG's potential would help meet an urgent clinical need within civilian, sports and military medicine.

Keywords: Magnetoencephalography, Mild traumatic brain injury, Systematic review

NeuroImage. Clinical (2021), Vol. 31 (34010785) (7 citations)

Magnetoencephalography in the Detection and Characterization of Brain Abnormalities Associated with Traumatic Brain Injury: A Comprehensive Review (2021)

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ABSTRACT Magnetoencephalography (MEG) is a functional brain imaging technique with high temporal resolution compared with techniques that rely on metabolic coupling. MEG has an important role in traumatic brain injury (TBI) research, especially in mild TBI, which may not have detectable features in conventional, anatomical imaging techniques. This review addresses the original research articles to date that have reported on the use of MEG in TBI. Specifically, the included studies have demonstrated the utility of MEG in the detection of TBI, characterization of brain connectivity abnormalities associated with TBI, correlation of brain signals with post-concussive symptoms, differentiation of TBI from post-traumatic stress disorder, and monitoring the response to TBI treatments. Although presently the utility of MEG is mostly limited to research in TBI, a clinical role for MEG in TBI may become evident with further investigation.

Keywords: concussion, functional neuroimaging, magnetoencephalography, traumatic brain injury

Medical sciences (Basel, Switzerland) (2021), Vol. 9, No. 1 (33557219) (1 citation)

Resting-state magnetoencephalography source magnitude imaging with deep-learning neural network for classification of symptomatic combat-related mild traumatic brain injury (2021)

Huang, Ming-Xiong; Huang, Charles W; Harrington, Deborah L; Robb-Swan, Ashley; Angeles-Quinto, Annemarie; Nichols, Sharon; Huang, Jeffrey W; Le, Lu; Rimmele, Carl; Matthews, Scott; Drake, Angela; Song, Tao; Ji, Zhengwei; Cheng, Chung-Kuan; Shen, Qian; Foote, Ericka; Lerman, Imanuel; Yurgil, Kate A; Hansen, Hayden B; Naviaux, Robert K; Dynes, Robert; Baker, Dewleen G; Lee, Roland R

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ABSTRACT Combat-related mild traumatic brain injury (cmTBI) is a leading cause of sustained physical, cognitive, emotional, and behavioral disabilities in Veterans and active-duty military personnel. Accurate diagnosis of cmTBI is challenging since the symptom spectrum is broad and conventional neuroimaging techniques are insensitive to the underlying neuropathology. The present study developed a novel deep-learning neural network method, 3D-MEGNET, and applied it to resting-state magnetoencephalography (rs-MEG) source-magnitude imaging data from 59 symptomatic cmTBI individuals and 42 combat-deployed healthy controls (HCs). Analytic models of individual frequency bands and all bands together were tested. The All-frequency model, which combined delta-theta (1-7 Hz), alpha (8-12 Hz), beta (15-30 Hz), and gamma (30-80 Hz) frequency bands, outperformed models based on individual bands. The optimized 3D-MEGNET method distinguished cmTBI individuals from HCs with excellent sensitivity (99.9 ± 0.38%) and specificity (98.9 ± 1.54%). Receiver-operator-characteristic curve analysis showed that diagnostic accuracy was 0.99. The gamma and delta-theta band models outperformed alpha and beta band models. Among cmTBI individuals, but not controls, hyper delta-theta and gamma-band activity correlated with lower performance on neuropsychological tests, whereas hypo alpha and beta-band activity also

correlated with lower neuropsychological test performance. This study provides an integrated framework for condensing large source-imaging variable sets into optimal combinations of regions and frequencies with high diagnostic accuracy and cognitive relevance in cmTBI. The all-frequency model offered more discriminative power than each frequency-band model alone. This approach offers an effective path for optimal characterization of behaviorally relevant neuroimaging features in neurological and psychiatric disorders.

Keywords: Veterans, delta rhythm, gamma rhythm, machine learning, military service members, neuropsychology, resting-state MEG, traumatic brain injury

Human brain mapping (2021), Vol. 42, No. 7 (33449442) (2 citations)

Interhemispheric differences in P1 and N1 amplitude in EEG and MEG differ across older individuals with a concussion compared with age-matched controls (2021)

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ABSTRACT We studied the effects of mild traumatic brain injury (mTBI) in an aging population. We examined visual search with event-related potentials (ERPs) and event-related fields (ERF) for a lateral color singleton focusing on the P1 and N1 in each hemisphere. Forty participants (19 mTBI and 21 controls) aged 50 to 72 performed a visual search task, while we recorded their magnetoencephalogram (MEG) with simultaneous electroencephalogram (EEG). We compared visual ERPs and ERFs and associated cortical activity estimated using MEG source localization. Relative to matched controls, participants with an mTBI had a smaller P1 in the left hemisphere and a smaller N1 in the right hemisphere. Also, mTBI participants showed inversed activation patterns across the hemispheres during the N1 in MEG compared with controls. This is the first study to investigate the impact of mTBI on neuronal source activations during early visual processing in an aging population. Results showed that when aging individuals suffer from an mTBI, there are perturbations in the amplitude and hemispheric dominance patterns in the visual P1 and N1 responses that are visible for months to years following the injury. Our findings indicate that mTBI can lead to modifications of sensory and/or perceptual responses, suggesting possible adaptive functional reorganization following mTBI.

Keywords: EEG, MEG, N1, P1, aging, concussion, mild traumatic brain injury (mTBI), visual ERP

Psychophysiology (2021), Vol. 58, No. 3 (33347633) (2 citations)

Portable neuromodulation induces neuroplasticity to re-activate motor function recovery from brain injury: a high-density MEG case study (2020)

D'Arcy, Ryan C N; Greene, Trevor; Greene, Debbie; Frehlick, Zack; Fickling, Shaun D; Campbell, Natasha; Etheridge, Tori; Smith, Christopher; Bollinger, Fabio; Danilov, Yuri; Livingstone, Ashley; Tannouri, Pamela; Martin, Pauline; Lakhani, Bimal

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BACKGROUND In a recent high-profile case study, we used functional magnetic resonance imaging (fMRI)

to monitor improvements in motor function related to neuroplasticity following rehabilitation for severe traumatic brain injury (TBI). The findings demonstrated that motor function improvements can occur years beyond current established limits. The current study extends the functional imaging investigation to characterize neuromodulation effects on neuroplasticity to further push the limits.

METHODS Canadian Soldier Captain (retired) Trevor Greene (TG) survived a severe open-TBI when attacked with an axe during a 2006 combat tour in Afghanistan. TG has since continued intensive daily rehabilitation to recover motor function, experiencing an extended plateau using conventional physical therapy. To overcome this plateau, we paired translingual neurostimulation (TLNS) with the continuing rehabilitation program.

RESULTS Combining TLNS with rehabilitation resulted in demonstrable clinical improvements along with corresponding changes in movement evoked electroencephalography (EEG) activity. High-density magnetoencephalography (MEG) characterized cortical activation changes in corresponding beta frequency range (27 Hz). MEG activation changes corresponded with reduced interhemispheric inhibition in the post-central gyri regions together with increased right superior/middle frontal activation suggesting large scale network level changes.

CONCLUSIONS The findings provide valuable insight into the potential importance of non-invasive neuromodulation to enhance neuroplasticity mechanisms for recovery beyond the perceived limits of rehabilitation.

Keywords: Brain vital signs, Electroencephalography (EEG), Functional connectivity, Magnetoencephalography (MEG), Motor function, Neuroplasticity, Portable neuromodulation stimulator (PoNS), Rehabilitation, Translingual neurostimulation (TLNS), Traumatic brain injury (TBI)

Journal of neuroengineering and rehabilitation (2020), Vol. 17, No. 1 (33261623) (6 citations)

Local and large-scale beta oscillatory dysfunction in males with mild traumatic brain injury (2020)

Zhang, Jing; Safar, Kristina; Emami, Zahra; Ibrahim, George M; Scratch, Shannon E; da Costa, Leodante; Dunkley, Benjamin T

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ABSTRACT Mild traumatic brain injury (mTBI) is impossible to detect with standard neuroradiological assessment such as structural magnetic resonance imaging (MRI). Injury does, however, disrupt the dynamic repertoire of neural activity indexed by neural oscillations. In particular, beta oscillations are reliable predictors of cognitive, perceptual, and motor system functioning, as well as correlating highly with underlying myelin architecture and brain connectivity-all factors particularly susceptible to dysregulation after mTBI. We measured local and large-scale neural circuit function by magnetoencephalography (MEG) with a data-driven model fit approach using the fitting oscillations and one-over f algorithm in a group of young adult men with mTBI and a matched healthy control group. We quantified band-limited regional power and functional connectivity between brain regions. We found reduced regional power and deficits in functional connectivity across brain areas, which pointed to the well-characterized thalamocortical dysconnectivity associated with mTBI. Furthermore, our results suggested that beta functional connectivity data reached the best mTBI classification performance compared with regional power and symptom severity [measured with Sport Concussion Assessment Tool 2 (SCAT2)]. The present study reveals the relevance of beta oscillations as a window into neurophysiological dysfunction in mTBI and also highlights the reliability of neural synchrony biomarkers in disorder classification.NEW & NOTEWORTHY Mild traumatic brain injury (mTBI) disrupts the dynamic repertoire of neural oscillations, but so far beta activity has not been studied. In mTBI, we found reductions in frontal beta and large-scale beta networks, indicative of thalamo-cortical dysconnectivity and disrupted information flow through cortico-basal ganglia-thalamic circuits. Relatively, connectivity more accurately classifies individual mTBI cases compared with regional power. We show the relevance of beta oscillations in mTBI and the reliability of these markers in classification.

Keywords: beta oscillations, concussion, machine learning, magnetoencephalography, neural activity

Journal of neurophysiology (2020), Vol. 124, No. 6 (33052746) (10 citations)

Magnetoencephalography for Mild Traumatic Brain Injury and Posttraumatic Stress Disorder (2020)

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ABSTRACT Mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD) are leading causes of sustained physical, cognitive, emotional, and behavioral deficits in the general population, active-duty military personnel, and veterans. However, the underlying pathophysiology of mTBI/PTSD and the mechanisms that support functional recovery for some, but not all individuals is not fully understood. Conventional MR imaging and computed tomography are generally negative in mTBI and PTSD, so there is interest in the development of alternative evaluative strategies. Of particular note are magnetoencephalography (MEG) -based methods, with mounting evidence that MEG can provide sensitive biomarkers for abnormalities in mTBI and PTSD.

Keywords: Functional connectivity, GABA-ergic, Gamma wave, Posttraumatic stress disorder, Slow wave, Traumatic brain injury

Neuroimaging clinics of North America (2020), Vol. 30, No. 2 (32336405) (4 citations)

Resting-State Magnetoencephalography Source Imaging Pilot Study in Children with Mild Traumatic Brain Injury (2020)

Huang, Ming-Xiong; Robb Swan, Ashley; Angeles Quinto, Annemarie; Huang, Jeffrey W; De-la-Garza, Bianca G; Huang, Charles W; Hesselink, John R; Bigler, Erin D; Wilde, Elisabeth A; Max, Jeffrey E

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ABSTRACT Mild traumatic brain injury (mTBI) accounts for the vast majority of all pediatric TBI. An important minority of children who have suffered an mTBI have enduring cognitive and emotional symptoms. However, the mechanisms of chronic symptoms in children with pediatric mTBI are not fully understood. This is in part due to the limited sensitivity of conventional neuroimaging technologies. The present study examined resting-state magnetoencephalography (rs-MEG) source images in 12 children who had mTBI and 12 age-matched control children. The rs-MEG exams were performed in children with mTBI 6 months after injury when they reported no clinically significant post-injury psychiatric changes and few if any somatic sensorimotor symptoms but did report cognitive symptoms. MEG source magnitude images were obtained for different frequency bands in alpha (8-12 Hz), beta (15-30 Hz), gamma (30-90 Hz), and low-frequency (1-7 Hz) bands.

In contrast to the control participants, rs-MEG source imaging in the children with mTBI showed: 1) hyperactivity from the bilateral insular cortices in alpha, beta, and low-frequency bands, from the left amygdala in alpha band, and from the left precuneus in beta band; 2) hypoactivity from the bilateral dorsolateral prefrontal cortices (dlPFC) in alpha and beta bands, from the ventromedial prefrontal cortex (vmPFC) in beta band, from the ventrolateral prefrontal cortex (vlPFC) in gamma band, from the anterior cingulate cortex (ACC) in alpha band, and from the right precuneus in alpha band. The present study showed that MEG source imaging technique revealed abnormalities in the resting-state electromagnetic signals from the children with mTBI.

Keywords: MEG, mild traumatic brain injury, pediatric, post-concussion symptoms, psychiatric disorder

Journal of neurotrauma (2020), Vol. 37, No. 7 (31724480) (5 citations)

Anomaly Detection of Moderate Traumatic Brain Injury Using Auto-Regularized Multi-Instance One-Class SVM (2020)

Rasheed, Waqas; Tang, Tong Boon

ABSTRACT Detection and quantification of functional deficits due to moderate traumatic brain injury (mTBI) is crucial for clinical decision-making and timely commencement of functional therapy. In this work, we explore magnetoencephalography (MEG) based functional connectivity features i.e. magnitude squared coherence (MSC) and phase lag index (PLI) to quantify synchronized brain activity patterns as a means to detect functional deficits. We propose a multi-instance one-class support vector machine (SVM) model generated from a healthy control population. Any dispersion from the decision boundary of the model would be identified as an anomaly instance of mTBI case (Glasgow Coma Scale, GCS score between 9 and 13). The decision boundary was optimized by considering the closest anomaly (GCS =13) from the negative class as a support vector. Validated against magnetic resonance imaging (MRI) data, the proposed model at high beta band yielded an accuracy of 94.19% and a sensitivity of 90.00%, when tested with our mTBI dataset. The results support the suggestion of multi-instance one-class SVM for the detection of mTBI.

IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society (2020), Vol. 28, No. 1 (31647439) (4 citations)

Marked Increases in Resting-State MEG Gamma-Band Activity in Combat-Related Mild Traumatic Brain Injury (2020)

Huang, Ming-Xiong; Huang, Charles W; Harrington, Deborah L; Nichols, Sharon; Robb-Swan, Ashley; Angeles-Quinto, Annemarie; Le, Lu; Rimmele, Carl; Drake, Angela; Song, Tao; Huang, Jeffrey W; Clifford, Royce; Ji, Zhengwei; Cheng, Chung-Kuan; Lerman, Imanuel; Yurgil, Kate A; Lee, Roland R; Baker, Dewleen G

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ABSTRACT Combat-related mild traumatic brain injury (mTBI) is a leading cause of sustained impairments in military service members and veterans. Recent animal studies show that GABA-ergic parvalbumin-positive interneurons are susceptible to brain injury, with damage causing abnormal increases in spontaneous gamma-band (30-80 Hz) activity. We investigated spontaneous gamma activity in individuals with mTBI using high-resolution resting-state magnetoencephalography source imaging. Participants included 25 symptomatic individuals with chronic combat-related blast mTBI and 35 healthy controls with similar combat experiences. Compared with controls, gamma activity was markedly elevated in mTBI participants throughout frontal, parietal, temporal, and occipital cortices, whereas gamma activity was reduced in ventromedial prefrontal cortex. Across groups, greater gamma activity correlated with poorer performances on tests of executive functioning and visuospatial processing. Many neurocognitive associations, however, were partly driven by the higher incidence of mTBI participants with both higher gamma activity and poorer cognition, suggesting that expansive upregulation of gamma has negative repercussions for cognition particularly in mTBI. This is the first human study to demonstrate abnormal resting-state gamma activity in mTBI. These novel findings suggest the possibility that abnormal gamma activities may be a proxy for GABA-ergic interneuron dysfunction and a promising neuroimaging marker of insidious mild head injuries.

Keywords: cognition, frontoparietal network, gamma activity, magnetoencephalography, mild traumatic brain injury

Cerebral cortex (New York, N.Y.: 1991) (2020), Vol. 30, No. 1 (31041986) (10 citations)

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