MEGIN

Book of Abstracts - MEG Studies

Magnetoencephalography 2017–2022

Forewords

Dear reader,

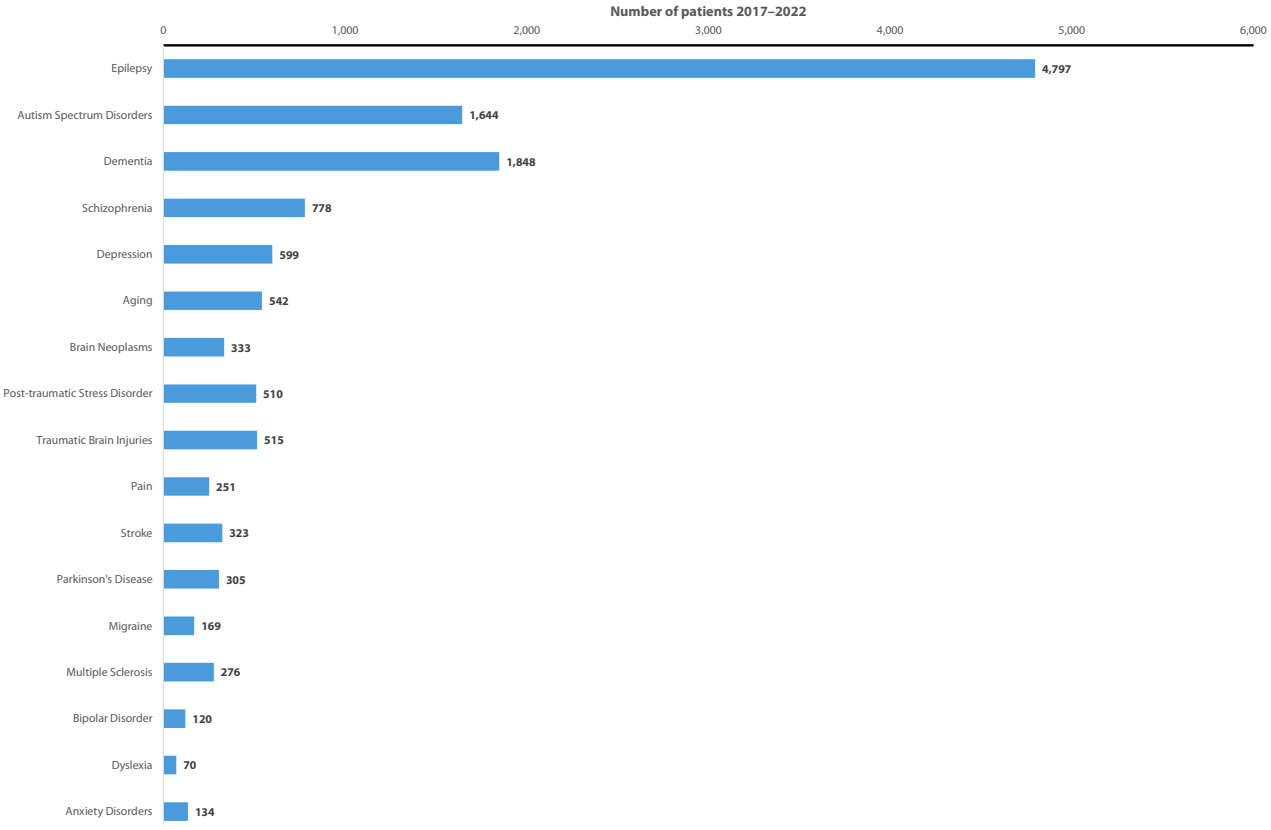
We are delighted about the number and high quality of magnetoencephalography (MEG) research published every year by MEGIN customers as well as by users of other MEG devices. While not a comprehensive bibliography of magnetoencephalography research, this book presents you with a selection of abstracts we believe reflect some of the more exciting and influential clinical research using this technology.

When selecting abstracts for this book, we reviewed 479 studies published from 2017 through 2022. These papers involved over 13,800 patients, spanning diseases such as epilepsy, dementias, autism spectrum disorders, and many more. 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.

We were astounded by the number of patients involved in research on epilepsy, autism spectrum disorders, dementias and many other disorders. The below chart indicates the number of patients involved in research into some of the most studied of these disorders and conditions during the past five years covered by this book.

Abstracts included on the following pages represent what we believe are the most influential studies in each disorder or condition. MEGIN does not, however, assume any responsibility for the content of the studies included in this book.

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 particular disorder.



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Aging

Spatiotemporal Oscillatory Patterns During Working Memory Maintenance in Mild Cognitive Impairment and Subjective Cognitive Decline (2020)

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ABSTRACT Working memory (WM) is a crucial cognitive process and its disruption is among the earliest symptoms of Alzheimer's disease. While alterations of the neuronal processes underlying WM have been evidenced in mild cognitive impairment (MCI), scarce literature is available in subjective cognitive decline (SCD). We used magnetoencephalography during a WM task performed by MCI (n = 45), SCD (n = 49) and healthy elders (n = 49) to examine group differences during the maintenance period (0-4000ms). Data were analyzed using time-frequency analysis and significant oscillatory differences were localized at the source level. Our results indicated significant differences between groups, mainly during the early maintenance (250-1250ms) in the theta, alpha and beta bands and in the late maintenance (2750-3750ms) in the theta band. MCI showed lower local synchronization in fronto-temporal cortical regions in the early theta-alpha window relative to controls (p = 2 × 10-03) and SCD (p = 4 × 10-03), and in the late theta window relative to controls (p = 1 × 1003) and SCD (p = 0.01). Early theta-alpha power was significantly correlated with memory scores (rho = 0.24,p = 0.02) and late theta power was correlated with task performance (rho = 0.24,p = 0.03) and functional activity scores (rho = -0.23,p = 0.02). In the early beta window, MCI showed reduced power in temporo-posterior regions relative to controls (p = 3 × 10-03) and SCD (p = 0.02). Our results may suggest that these alterations would reflect that memory-related networks are damaged.

Keywords: Alzheimer's disease (AD), Induced oscillatory activity, magnetoencephalography (MEG), mild cognitive impairment (MCI), subjective cognitive decline (SCD), working memory (WM)

International journal of neural systems (2020), Vol. 30, No. 1 (31522594)

The impact of age and sex on the oscillatory dynamics of visuospatial processing (2019)

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ABSTRACT The ability to dynamically allocate neural resources within the visual space is supported by a number of spectrally-specific oscillatory responses, and such visuospatial processing has been found to decline moderately with age and differ by sex. However, the direct effects of age and sex on these oscillatory dynamics remains poorly understood. Using magnetoencephalography (MEG), structural magnetic resonance imaging, and advanced source reconstruction and statistical methods, we investigated the impact of aging and sex on behavioral performance and the underlying neural dynamics during visuospatial processing. In a large sample spanning a broad age range, we find that a number of prototypical attention

and perception network components, both spectrally- and spatially-defined, exhibit complex and uniquely informative relationships with age and sex. Specifically, neural responses in the theta range (4-10 Hz) were found to covary with chronological age in prefrontal and motor cortices, signifying a possible relationship between age and cognitive control. Further, we found that beta (18-24 Hz) activity covaried with age across a large swath of the somato-motor strip, supporting previous findings of motor planning and execution deficits with increasing age. Finally, gamma-frequency (48-70 Hz) oscillations were found to exhibit robust covariance with age in superior parietal and temporo-parietal areas, indicating that the mapping of saliency in visual space is modulated by the normal aging process. Interestingly, behavioral performance and some of these oscillatory neural responses also exhibited interactions between age and sex, indicating sex differences in the evolution of the neural coding of visual perception as age increases. In particular, men were found to have stronger correlations between age and neural oscillatory responses during task performance than women in lateral occipital and superior temporal regions in the alpha band and in dorsolateral prefrontal cortex in the gamma band, while women exhibited more robust covariance between age and neural responses than men in inferior temporal and medial prefrontal cortex in the theta range.

Keywords: Aging, Attention, Neural oscillations, Sex differences

NeuroImage (2019), Vol. 185 (30321644)

Anticipatory neural dynamics of spatial-temporal orienting of attention in younger and older adults (2019)

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ABSTRACT Spatial and temporal expectations act synergistically to facilitate visual perception. In the current study, we sought to investigate the anticipatory oscillatory markers of combined spatial-temporal orienting and to test whether these decline with ageing. We examined anticipatory neural dynamics associated with joint spatial-temporal orienting of attention using magnetoencephalography (MEG) in both younger and older adults. Participants performed a cued covert spatial-temporal orienting task requiring the discrimination of a visual target. Cues indicated both where and when targets would appear. In both age groups, valid spatial-temporal cues significantly enhanced perceptual sensitivity and reduced reaction times. In the MEG data, the main effect of spatial orienting was the lateralised anticipatory modulation of posterior alpha and beta oscillations. In contrast to previous reports, this modulation was not attenuated in older adults; instead it was even more pronounced. The main effect of temporal orienting was a bilateral suppression of posterior alpha and beta oscillations. This effect was restricted to younger adults. Our results also revealed a striking interaction between anticipatory spatial and temporal orienting in the gamma-band (60-75 Hz). When considering both age groups separately, this effect was only clearly evident and only survived statistical evaluation in the older adults. Together, these observations provide several new insights into the neural dynamics supporting separate as well as combined effects of spatial and temporal orienting of attention, and suggest that different neural dynamics associated with attentional orienting appear differentially sensitive to ageing.

Keywords: Ageing, Anticipatory attention, MEG, Oscillations, Spatial orienting, Temporal orienting

NeuroImage (2018), Vol. 178 (29733953)

Maturation trajectories of cortical resting-state networks depend on the mediating frequency band (2019)

Khan, Sheraz; Hashmi, Javeria A; Mamashli, Fahimeh; Michmizos, Konstantinos; Kitzbichler, Manfred G; Bharadwaj, Hari; Bekhti, Yousra; Ganesan, Santosh; Garel, Keri-Lee A; Whitfield-Gabrieli, Susan; Gollub, Randy L; Kong, Jian; Vaina, Lucia M; Rana, Kunjan D; Stufflebeam, Steven M; Hämäläinen, Matti S; Kenet, Tal

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ABSTRACT The functional significance of resting state networks and their abnormal manifestations in psychiatric disorders are firmly established, as is the importance of the cortical rhythms in mediating these networks. Resting state networks are known to undergo substantial reorganization from childhood to adulthood, but whether distinct cortical rhythms, which are generated by separable neural mechanisms and are often manifested abnormally in psychiatric conditions, mediate maturation differentially, remains unknown. Using magnetoencephalography (MEG) to map frequency band specific maturation of resting state networks from age 7 to 29 in 162 participants (31 independent), we found significant changes with age in networks mediated by the beta (13-30 Hz) and gamma (31-80 Hz) bands. More specifically, gamma band mediated networks followed an expected asymptotic trajectory, but beta band mediated networks followed a linear trajectory. Network integration increased with age in gamma band mediated networks, while local segregation increased with age in beta band mediated networks. Spatially, the hubs that changed in importance with age in the beta band mediated networks had relatively little overlap with those that showed the greatest changes in the gamma band mediated networks. These findings are relevant for our understanding of the neural mechanisms of cortical maturation, in both typical and atypical development.

Keywords: Brain connectivity, Development, Graph theory, Magnetoencephalography, Rhythms

NeuroImage (2018), Vol. 174 (29462724)

Aging Affects Adaptation to Sound-Level Statistics in Human Auditory Cortex (2019)

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ABSTRACT Optimal perception requires efficient and adaptive neural processing of sensory input. Neurons in nonhuman mammals adapt to the statistical properties of acoustic feature distributions such that they become sensitive to sounds that are most likely to occur in the environment. However, whether human auditory responses adapt to stimulus statistical distributions and how aging affects adaptation to stimulus statistics is unknown. We used MEG to study how exposure to different distributions of sound levels affects adaptation in auditory cortex of younger (mean: 25 years; n = 19) and older (mean: 64 years; n = 20) adults (male and female). Participants passively listened to two sound-level distributions with different modes (either 15 or 45 dB sensation level). In a control block with long interstimulus intervals, allowing neural populations to recover from adaptation, neural response magnitudes were similar between younger and older adults. Critically, both age groups demonstrated adaptation to sound-level stimulus statistics, but adaptation was altered for older compared with younger people: in the older group, neural responses continued to be sensi-

tive to sound level under conditions in which responses were fully adapted in the younger group. The lack of full adaptation to the statistics of the sensory environment may be a physiological mechanism underlying the known difficulty that older adults have with filtering out irrelevant sensory information.SIGNIFICANCE STATEMENT Behavior requires efficient processing of acoustic stimulation. Animal work suggests that neurons accomplish efficient processing by adjusting their response sensitivity depending on statistical properties of the acoustic environment. Little is known about the extent to which this adaptation to stimulus statistics generalizes to humans, particularly to older humans. We used MEG to investigate how aging influences adaptation to sound-level statistics. Listeners were presented with sounds drawn from sound-level distributions with different modes (15 vs 45 dB). Auditory cortex neurons adapted to sound-level statistics in younger and older adults, but adaptation was incomplete in older people. The data suggest that the aging auditory system does not fully capitalize on the statistics available in sound environments to tune the perceptual system dynamically.

Keywords: aging, auditory cortex, magnetoencephalography, neural adaptation, stimulus statistics

The Journal of neuroscience: the official journal of the Society for Neuroscience (2018), Vol. 38, No. 8 (29358362)

Brain structure and verbal function across adulthood while controlling for cerebrovascular risks

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ABSTRACT The development and decline of brain structure and function throughout adulthood is a complex issue, with cognitive aging trajectories influenced by a host of factors including cerebrovascular risk. Neuroimaging studies of age-related cognitive decline typically reveal a linear decrease in gray matter (GM) volume/density in frontal regions across adulthood. However, white matter (WM) tracts mature later than GM, particularly in regions necessary for executive functions and memory. Therefore, it was predicted that a middle-aged group (MC: 35-45 years) would perform best on a verbal working memory task and reveal greater regional WM integrity, compared with both young (YC: 18-25 years) and elder groups (EC: 60+ years). Diffusion tensor imaging (DTI) and magnetoencephalography (MEG) were obtained from 80 healthy participants. Objective measures of cerebrovascular risk and cognition were also obtained. As predicted, MC revealed best verbal working memory accuracy overall indicating some maturation of brain function between YC and MC. However, contrary to the prediction fractional anisotropy values (FA), a measure of WM integrity, were not greater in MC (i.e., there were no significant differences in FA between YC and MC but both groups showed greater FA than EC). An overall multivariate model for MEG ROIs showed greater peak amplitudes for MC and YC, compared with EC. Subclinical cerebrovascular risk factors (systolic blood pressure and blood glucose) were negatively associated with FA in frontal callosal, limbic, and thalamic radiation regions which correlated with executive dysfunction and slower processing speed, suggesting their contribution to age-related cognitive decline. Hum Brain Mapp 38:3472-3490, 2017. © 2017 Wiley Periodicals, Inc.

Keywords: DTI, MEG, blood pressure, blood sugar, cerebrovascular risk, development, fractional anisotropy, normal aging, verbal memory, working memory

Human brain mapping (2017), Vol. 38, No. 7 (28390167)

Amyotrophic Lateral Sclerosis

Altered cortical beta-band oscillations reflect motor system degeneration in amyotrophic lateral sclerosis (2018)

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ABSTRACT Continuous rhythmic neuronal oscillations underpin local and regional cortical communication. The impact of the motor system neurodegenerative syndrome amyotrophic lateral sclerosis (ALS) on the neuronal oscillations subserving movement might therefore serve as a sensitive marker of disease activity. Movement preparation and execution are consistently associated with modulations to neuronal oscillation beta (15-30 Hz) power. Cortical beta-band oscillations were measured using magnetoencephalography (MEG) during preparation for, execution, and completion of a visually cued, lateralized motor task that included movement inhibition trials. Eleven "classical" ALS patients, 9 with the primary lateral sclerosis (PLS) phenotype, and 12 asymptomatic carriers of ALS-associated gene mutations were compared with age-similar healthy control groups. Augmented beta desynchronization was observed in both contra- and ipsilateral motor cortices of ALS patients during motor preparation. Movement execution coincided with excess beta desynchronization in asymptomatic mutation carriers. Movement completion was followed by a slowed rebound of beta power in all symptomatic patients, further reflected in delayed hemispheric lateralization for beta rebound in the PLS group. This may correspond to the particular involvement of interhemispheric fibers of the corpus callosum previously demonstrated in diffusion tensor imaging studies. We conclude that the ALS spectrum is characterized by intensified cortical beta desynchronization followed by delayed rebound, concordant with a broader concept of cortical hyperexcitability, possibly through loss of inhibitory interneuronal influences. MEG may potentially detect cortical dysfunction prior to the development of overt symptoms, and thus be able to contribute to the assessment of future neuroprotective strategies. Hum Brain Mapp 38:237-254, 2017. © 2016 Wiley Periodicals, Inc.

Keywords: biomarker, inhibition, magnetoencephalography, motor neurone disease, neuroimaging, neurophysiology

Human brain mapping (2017), Vol. 38, No. 1 (27623516)

Anxiety Disorders

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)

Altered resting-state functional connectivity in patients with obsessive-compulsive disorder: A magnetoencephalography study (2018)

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ABSTRACT Aberrant cortical-striatal-thalamic-cortical circuits have been implicated in the pathophysiology of obsessive-compulsive disorder (OCD). However, the neurobiological basis of OCD remains unclear. We compared patterns of functional connectivity in patients with OCD and in healthy controls using resting-state magnetoencephalography (MEG). Participants comprised 24 patients with OCD (21 men, 3 women) and 22 age- and sex-matched healthy controls (19 men, 3 women). Resting-state measurements were obtained over a 6-min period using a 152-channel whole-head MEG system. We examined group differences in oscillatory activity and distribution of functional cortical hubs based on the nodal centrality of phase-locking value (PLV) maps. Differences in resting-state functional connectivity were examined through PLV analysis in selected regions of interest based on these two findings. Patients with OCD demonstrated significantly lower delta band activity in the cortical regions of the limbic lobe, insula, orbitofrontal, and temporal regions, and theta band activity in the parietal lobe regions than healthy controls. Patients with OCD exhibited fewer functional hubs in the insula and orbitofrontal cortex and additional hubs in the cingulate and temporoparietal regions. The OCD group exhibited significantly lower phase synchronization among the insula, orbitofrontal cortex, and cortical regions of the limbic lobe in all band frequencies, except in the delta band. Altered functional networks in the resting state may be associated with the pathophysiology of OCD. These MEG findings indicate that OCD is associated with decreased functional connectivity in terms of phase synchrony, particularly in the insula, orbitofrontal cortex, and cortical regions of the limbic lobe.

Keywords: Functional hub, Magnetoencephalography, Obsessive-compulsive disorder (OCD), Phase-locking value, Resting-state functional connectivity, Synchronization

International journal of psychophysiology: official journal of the International Organization of Psychophysiology (2018), Vol. 123 (29107610)

Commonalities and differences in the neural substrates of threat predictability in panic disorder and specific phobia (2017)

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ABSTRACT Different degrees of threat predictability are thought to induce either phasic fear or sustained anxiety. Maladaptive, sustained anxious apprehension is thought to result in overgeneralization of anxiety and thereby to contribute to the development of anxiety disorders. Therefore, differences in threat predictability have been associated with pathological states of anxiety with specific phobia (SP) representing phasic fear as heightened response to predictable threat, while panic disorder (PD) is characterized by sustained anxiety (unpredictable threat) and, as a consequence, overgeneralization of fear. The present study aimed to delineate commonalities and differences in the neural substrates of the impact of threat predictability on affective processing in these two anxiety disorders. Twenty PD patients, 20 SP patients and 20 non-anxious control subjects were investigated with an adapted NPU-design (no, predictable, unpredictable threat) using whole-head magnetoencephalography (MEG). Group independent neural activity in the right dlPFC increased with decreasing threat predictability. PD patients showed a sustained hyperactivation of the vmPFC under threat and safety conditions. The magnitude of hyperactivation was inversely correlated with PDs subjective arousal and anxiety sensitivity. Both PD and SP patients revealed decreased parietal processing of affective stimuli. Findings indicate overgeneralization between threat and safety conditions and increased need for emotion regulation via the vmPFC in PD, but not SP patients. Both anxiety disorders showed

decreased activation in parietal networks possibly indicating attentional avoidance of affective stimuli. Present results complement findings from fear conditioning studies and underline overgeneralization of fear, particularly in PD.

Keywords: Anxiety, Dorsolateral prefrontal cortex, MEG, Panic disorder, Ventromedial prefrontal cortex

NeuroImage. Clinical (2017), Vol. 14 (28331799)

Hypervigilance-avoidance in children with anxiety disorders: magnetoencephalographic evidence (2017)

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BACKGROUND An altered pattern of threat processing is deemed critical for the development of anxiety disorders (AD). According to the hypervigilance-avoidance hypothesis, AD patients show hypervigilance to threat cues at early stages of processing but avoid threat cues at later stages of processing. Consistently, adults with AD show enhanced neurophysiological responses to threat in early time windows and reduced responses to threat in late time windows. The presence of such a hypervigilance-avoidance effect and its underlying neural sources remain to be determined in clinically anxious children.

METHODS Twenty-three children diagnosed with an AD and 23 healthy control children aged 8-14 years saw faces with angry and neutral expressions while whole-head magnetoencephalography (MEG) was recorded. Neural sources were estimated based on L2-Minimum Norm inverse source modeling and analyzed in early, midlatency, and late time windows.

RESULTS In visual cortical regions, early threat processing was relatively enhanced in patients compared to controls, whereas this relation was inverted in a late interval. Consistent with the idea of affective regulation, the right dorsolateral prefrontal cortex revealed relatively reduced inhibition of early threat processing but revealed enhanced inhibition at a late interval in patients. Both visual-sensory and prefrontal effects were correlated with individual trait anxiety.

CONCLUSIONS These results support the hypothesis of early sensory hypervigilance followed by later avoidance of threat in anxiety disordered children, presumably modulated by early reduced and later enhanced prefrontal inhibition. This neuronal hypervigilance-avoidance pattern unfolds gradually with increasing trait anxiety, reflecting a progressively biased allocation of attention to threat.

Keywords: Anxiety disorders, avoidance, children, hypervigilance, magnetoencephalography, threat bias

Journal of child psychology and psychiatry, and allied disciplines (2017), Vol. 58, No. 1 (27605124)

Aphasia

Auditory training changes temporal lobe connectivity in 'Wernicke's aphasia': a randomised trial (2017)

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INTRODUCTION Aphasia is one of the most disabling sequelae after stroke, occurring in 25%-40% of stroke survivors. However, there remains a lack of good evidence for the efficacy or mechanisms of speech comprehension rehabilitation.

TRIAL DESIGN This within-subjects trial tested two concurrent interventions in 20 patients with chronic aphasia with speech comprehension impairment following left hemisphere stroke: (1) phonological training using 'Earobics' software and (2) a pharmacological intervention using donepezil, an acetylcholinesterase inhibitor. Donepezil was tested in a double-blind, placebo-controlled, cross-over design using block randomisation with bias minimisation.

METHODS The primary outcome measure was speech comprehension score on the comprehensive aphasia test. Magnetoencephalography (MEG) with an established index of auditory perception, the mismatch negativity response, tested whether the therapies altered effective connectivity at the lower (primary) or higher (secondary) level of the auditory network.

RESULTS Phonological training improved speech comprehension abilities and was particularly effective for patients with severe deficits. No major adverse effects of donepezil were observed, but it had an unpredicted negative effect on speech comprehension. The MEG analysis demonstrated that phonological training increased synaptic gain in the left superior temporal gyrus (STG). Patients with more severe speech comprehension impairments also showed strengthening of bidirectional connections between the left and right STG.

CONCLUSIONS Phonological training resulted in a small but significant improvement in speech comprehension, whereas donepezil had a negative effect. The connectivity results indicated that training reshaped higher order phonological representations in the left STG and (in more severe patients) induced stronger interhemispheric transfer of information between higher levels of auditory cortex.Clinical trial registrationThis trial was registered with EudraCT (2005-004215-30, https://eudract.ema.europa.eu/) and ISRCTN (68939136, http://www.isrctn.com/).

Keywords: Wernicke's aphasia, magnetoencephalography, pharmacological trial, phonological training, speech comprehension

Journal of neurology, neurosurgery, and psychiatry (2017), Vol. 88, No. 7 (28259857)

Attention Deficit Hyperactivity Disorder

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)

Autism Spectrum Disorders

Significance of Beta-Band Oscillations in Autism Spectrum Disorders During Motor Response Inhibition Tasks: A MEG Study (2021)

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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)

Delayed Auditory Evoked Responses in Autism Spectrum Disorder across the Life Span (2020)

Matsuzaki, Junko; Ku, Matthew; Dipiero, Marissa; Chiang, Taylor; Saby, Joni; Blaskey, Lisa; Kuschner, Emily S; Kim, Mina; Berman, Jeffrey I; Bloy, Luke; Chen, Yu-Han; Dell, John; Liu, Song; Brodkin, Edward S; Embick, David; Roberts, Timothy P L

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ABSTRACT The M50 and M100 auditory evoked responses reflect early auditory processes in the primary/secondary auditory cortex. Although previous M50 and M100 studies have been conducted on individuals with autism spectrum disorder (ASD) and indicate disruption of encoding simple sensory information, analogous investigations of the neural correlates of auditory processing through development from children into adults are very limited. Magnetoencephalography was used to record signals arising from the left and right superior temporal gyrus during auditory presentation of tones to children/adolescents and adults with ASD as well as typically developing (TD) controls. One hundred and thirty-two participants (aged 6-42 years) were included into the final analyses (children/adolescents: TD, n = 36, 9.21 ± 1.6 years; ASD, n = 58, 10.07 ± 2.38 years; adults: TD, n = 19, 26.97 ± 1.29 years; ASD, n = 19, 23.80 ± 6.26 years). There were main effects of group on M50 and M100 latency ($p < 0.001$) over hemisphere and frequency. Delayed M50 and M100 latencies were found in participants with ASD compared to the TD group, and earlier M50 and M100 latencies were associated with increased age. Furthermore, there was a statistically significant association between language ability and both M50 and M100 latencies. Importantly, differences in M50 and M100 latencies between TD and ASD cohorts, often reported in children, persisted into adulthood, with no evidence supporting latency convergence.

Keywords: Autism spectrum disorder, Language ability, Life span, M100, M50, Magnetoencephalography, Tones

Developmental neuroscience (2019), Vol. 41, No. 3-4 (32007990)

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)

Delayed M50/M100 evoked response component latency in minimally verbal/nonverbal children who have autism spectrum disorder (2020)

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ABSTRACT Abnormal auditory neuromagnetic M50 and M100 responses, reflecting primary/secondary auditory cortex processing, have been reported in children who have autism spectrum disorder (ASD). Some studies have reported an association between delays in these responses and language impairment. However, as most prior research has focused on verbal individuals with ASD without cognitive impairment, rather little is known about neural activity during auditory processing in minimally verbal or nonverbal children who have ASD (ASD-MVNV)-children with little or no speech and often significant cognitive impairment. To understand the neurophysiological mechanisms underlying auditory processing in ASD-MVNV children, magnetoencephalography (MEG) measured M50 and M100 responses arising from left and right superior temporal gyri during tone stimuli in three cohorts: (1) MVNV children who have ASD (ASD-MVNV), (2) verbal children who have ASD and no intellectual disability (ASD-V), and (3) typically developing (TD) children. One hundred and five participants (8-12 years) were included in the final analyses (ASD-MVNV: n = 16, 9.85 ± 1.32 years; ASD-V: n = 55, 10.64 ± 1.31 years; TD: n = 34, 10.18 ± 1.36 years). ASD-MVNV children showed significantly delayed M50 and M100 latencies compared to TD. These delays tended to be greater than the corresponding delays in verbal children with ASD. Across cohorts, delayed latencies were associated with language and communication skills, assessed by the Vineland Adaptive Behavior Scale Communication Domain. Findings suggest that auditory cortex neural activity measures could be dimensional objective indices of language impairment in ASD for either diagnostic (e.g., via threshold or cutoff) or prognostic (considering the continuous variable) use.

Keywords: Auditory cortex, Autism spectrum disorder, M50/M100 responses and language impairment, Magnetoencephalography, Minimally verbal/non-verbal children, Nonverbal

Molecular autism (2019), Vol. 10 (31428297)

Magnetoencephalographic (MEG) brain activity during a mental flexibility task suggests some shared neurobiology in children with neurodevelopmental disorders (2020)

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BACKGROUND Children with neurodevelopmental disorders (NDDs) exhibit a shared phenotype that involves executive dysfunctions including impairments in mental flexibility (MF). It is of interest to understand if this phenotype stems from some shared neurobiology.

METHODS To investigate this possibility, we used magnetoencephalography (MEG) neuroimaging to compare brain activity in children (n = 88; 8-15 years) with autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), as they completed a set-shifting/mental flexibility task.

RESULTS Neuroimaging results revealed a similar parietal activation profile across the NDD, groups suggesting a link to their shared phenotype. Differences in frontal activity differentiated the three clinical groups. Brain-behaviour analyses showed a link with repetitive behaviours suggesting shared dysfunction in the associative loop of the corticostriatal system.

CONCLUSION Our study supports the notion that NDDs may exist along a complex phenotypic/biological continuum. All NDD groups showed a sustained parietal activity profile suggesting that they share a strong reliance on the posterior parietal cortices to complete

the mental flexibility task; future studies could elucidate whether this is due to delayed brain development or compensatory functioning. The differences in frontal activity may play a role in differentiating the NDDs. The OCD group showed sustained prefrontal activity that may be reflective of hyperfrontality. The ASD group showed reduced frontal activation suggestive of frontal dysfunction and the ADHD group showed an extensive hypoactivity that included frontal and parietal regions. Brain-behaviour analyses showed a significant correlation with repetitive behaviours which may reflect dysfunction in the associative loop of the corticostriatal system, linked to inflexible behaviours.

Keywords: ADHD, ASD, Corticostriatal projections, Executive function, MEG, Neurodevelopmental disorders, OCD, RBS-R, Set shifting, TOCS

Journal of neurodevelopmental disorders (2019), Vol. 11, No. 1 (31426750)

Abnormal Auditory Mismatch Fields in Children and Adolescents with 47,XYY Syndrome (2020)

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ABSTRACT 47,XYY syndrome (XYY) is one of the common forms of sex chromosome aneuploidy in males. XYY males tend to have tall stature, early speech, motor delays, social and behavioral challenges, and a high rate of language impairment. Recent studies indicate that 20-40% of males with XYY meet diagnostic criteria for autism spectrum disorder (ASD; the rate in the general population is 1-2%). Although many studies have examined the neural correlates of language impairment in ASD, few similar studies have been conducted on individuals with XYY. Studies using magnetoencephalography (MEG) in idiopathic ASD (ASD-I) have demonstrated delayed neurophysiological responses to changes in the auditory stream, revealed in the mismatch negativity or its magnetic counterpart, the mismatch field (MMF). This study investigated whether similar findings are observed in XYY-associated ASD and whether delayed processing is also present in individuals with XYY without ASD. MEG measured MMFs arising from the left and the right superior temporal gyrus during an auditory oddball paradigm with vowel stimuli (/a/ and /u/) in children/adolescents with XYY both with and without a diagnosis of ASD, as well as in those with ASD-I and in typically developing controls (TD). Ninety male participants (6-17 years old) were included in the final analyses (TD, n = 38, 11.50 ± 2.88 years; ASD-I, n = 21, 13.83 ± 3.25 years; XYY without ASD, n = 15, 12.65 ± 3.91 years; XYY with ASD, n = 16, 12.62 ± 3.19 years). The groups did not differ significantly in age ($p > 0.05$). There was a main effect of group on MMF latency ($p < 0.001$). Delayed MMF latencies were found in participants with XYY both with and without an ASD diagnosis, as well as in the ASD-I group compared to the TD group (ps < 0.001). Furthermore, participants with XYY (with and without ASD) showed a longer MMF latency than the ASD-I group (ps < 0.001). There was, however, no significant difference in MMF latency between individuals with XYY with ASD and those with XYY without ASD. Delayed MMF latencies were associated with severity of language impairment. Our findings suggest that auditory MMF latency delays are pronounced in this specific Y chromosome aneuploidy disorder, both with and without an ASD diagnosis, and thus may implicate the genes of the Y chromosome in mediating atypical MMF activity.

Keywords: Autism spectrum disorder, Language impairment, Magnetoencephalography, Vowel mismatch fields, XYY syndrome

Developmental neuroscience (2019), Vol. 41, No. 1-2 (31280271)

Sensorimotor Cortical Oscillations during Movement Preparation in 16p11.2 Deletion Carriers (2020)

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ABSTRACT Sensorimotor deficits are prevalent in many neurodevelopmental disorders like autism, including one of its common genetic etiologies, a 600 kb reciprocal deletion/duplication at 16p11.2. We have previously shown that copy number variations of 16p11.2 impact regional brain volume, white matter integrity, and early sensory responses in auditory cortex. Here, we test the hypothesis that abnormal cortical neurophysiology is present when genes in the 16p11.2 region are haploinsufficient, and in humans that this in turn may account for behavioral deficits specific to deletion carriers. We examine sensorimotor cortical network activity in males and females with 16p11.2 deletions compared with both typically developing individuals, and those with duplications of 16p11.2, using magnetoencephalographic imaging during preparation of overt speech or hand movements in tasks designed to be easy for all participants. In deletion carriers, modulation of beta oscillations (12-30 Hz) were increased during both movement types over effector-specific regions of motor cortices compared with typically developing individuals or duplication carriers, with no task-related performance differences between cohorts, even when corrected for their own cognitive and sensorimotor deficits. Reduced left hemispheric language specialization was observed in deletion carriers but not in duplication carriers. Neural activity over sensorimotor cortices in deletion carriers was linearly related to clinical measures of speech and motor impairment. These findings link insufficient copy number repeats at 16p11.2 to excessive neural activity (e.g., increased beta oscillations) in motor cortical networks for speech and hand motor control. These results have significant implications for understanding the neural basis of autism and related neurodevelopmental disorders.SIGNIFICANCE STATEMENT The recurrent 600 kb deletion at 16p11.2 (BP4-BP5) is one of the most common genetic etiologies of ASD and, more generally, of neurodevelopmental disorders. Here, we use high-resolution magnetoencephalographic imaging (MEG-I) to define with millisecond precision the underlying neurophysiological signature of motor impairments for individuals with 16p11.2 deletions. We identify significant increases in beta (12-30 Hz) suppression in sensorimotor cortices related to performance during speech and hand movement tasks. These findings not only provide a neurophysiological phenotype for the clinical presentation of this genetic deletion, but also guide our understanding of how genetic variation encodes for neural oscillatory dynamics.

Keywords: 16p11.2, autism, beta rhythm, magnetoencephalography, manual, speech

The Journal of neuroscience: the official journal of the Society for Neuroscience (2019), Vol. 39, No. 37 (31270155)

Lesser suppression of response to bright visual stimuli and visual abnormality in children with autism spectrum disorder: a magnetoencephalographic study (2020)

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BACKGROUND Visual abnormality is a common sensory impairment in autism spectrum disorder (ASD),

which may cause behavioral problems. However, only a few studies exist on the neural features corresponding to the visual symptoms in ASD. The purpose of this study was to investigate the relationship between cortical responses to visual stimuli and visual abnormality to examine the neurophysiological mechanisms of the visual abnormality in ASD.

METHODS Twenty-two high-functioning children with ASD (10.95 ± 2.01 years old) and 23 age-matched typically developing (TD) children (10.13 ± 2.80 years old) participated in this study. We measured the cortical responses (i.e., activated intensity and attenuation ratio) elicited by the Original visual image and other two types of bright images (the Dot noise or Blind image, which includes overlapped particles onto the Original image or the enhanced-brightness version of the Original image, respectively) using magnetoencephalography.

RESULTS The severity of visual abnormalities was significantly associated with behavioral problems in children with ASD. In addition, we found the increased cortical activation in response to the Original image in the left supramarginal gyrus (SMG) and middle temporal gyrus in children with ASD. However, there were no inter-group differences in the primary visual and medial orbitofrontal cortices. Furthermore, when we compared cortical responses according to the type of images, children with ASD showed lesser attenuation of the activated intensities than children with TD in response to the bright images compared with the Original image in the right SMG. These attenuation ratios (Dot noise/Original and Blind/Original) were also associated with the severity of visual abnormalities.

CONCLUSIONS Our results show that dysfunction of stimulus-driven neural suppression plays a crucial role in the neural mechanism of visual abnormality in children with ASD. To the best of our knowledge, this is the first magnetoencephalography study to demonstrate the association between the severity of visual abnormality and lower attenuation ratios in children with ASD. Our results contribute to the knowledge of the mechanisms underlying visual abnormality in children with ASD, and may therefore lead to more effective diagnosis and earlier intervention.

Keywords: Autism spectrum disorders (ASD), Bright visual stimuli, Magnetoencephalography (MEG), Neural suppression, Supramarginal gyrus (SMG), Visual abnormality

Journal of neurodevelopmental disorders (2019), Vol. 11, No. 1 (31200639)

Happy and Angry Faces Elicit Atypical Neural Activation in Children With Autism Spectrum Disorder (2020)

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BACKGROUND Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by significant impairments in social interactions and communication. The ability to accurately perceive and interpret emotional faces is critical to successful social interactions. However, few studies have investigated the spatiotemporal profile of the neural mechanisms underlying emotional face processing in ASD, particularly in children. The current study fills this important gap.

METHODS Participants were 55 children: 28 children with ASD (mean age = 9.5 ± 1.3 years) and 27 control children (mean age = 8.5 ± 1.3 years). All children completed an implicit emotional face task while mag-

netoencephalography was recorded. We examined spatiotemporal differences between the groups in neural activation during implicit processing of emotional faces.

RESULTS Within-group analyses demonstrated greater right middle temporal (300-375 ms) and superior temporal (300-400 ms) activation to angry faces than to happy faces in control children, while children with ASD showed greater activation from 250 to 500 ms to happy faces than to angry faces across frontal and temporal regions. Between-group analyses demonstrated that children with ASD showed similar patterns of late (425-500 ms) posterior cingulate and thalamic underactivity to both angry and happy faces relative to control children, suggesting general atypical processing of emotional information.

CONCLUSIONS Atypical posterior cingulate cortex and thalamus recruitment in children with ASD to emotional faces suggests poor modulation of toggling between the default mode network and task-based processing. Increased neural activity to happy faces compared with angry faces in children with ASD suggests reduced salience or immature response to anger, which in turn could contribute to deficits in social cognition in ASD.

Keywords: Autism spectrum disorder, Children, Emotional face processing, Magnetoencephalography, Neuroimaging, Social cognition

Biological psychiatry. Cognitive neuroscience and neuroimaging (2019), Vol. 4, No. 12 (31171500)

Abnormal auditory mismatch fields are associated with communication impairment in both verbal and minimally verbal/nonverbal children who have autism spectrum disorder (2020)

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ABSTRACT Abnormal auditory discrimination neural processes, indexed by mismatch fields (MMFs) recorded by magnetoencephalography (MEG), have been reported in verbal children with ASD. Association with clinical measures indicates that delayed MMF components are associated with poorer language and communication performance. At present, little is known about neural correlates of language and communication skills in extremely language impaired (minimally-verbal/non-verbal) children who have ASD: ASD-MVNV. It is hypothesized that MMF delays observed in language-impaired but nonetheless verbal children with ASD will be exacerbated in ASD-MVNV. The present study investigated this hypothesis, examining MMF responses bilaterally during an auditory oddball paradigm with vowel stimuli in ASD-MVNV, in a verbal ASD cohort without cognitive impairment and in typically developing (TD) children. The verbal ASD cohort without cognitive impairment was split into those demonstrating considerable language impairment (CELF core language index <85; "ASD-LI") versus those with less or no language impairment (CELF CLI >85; "ASD-V"). Eighty-four participants (8-12 years) were included in final analysis: ASD-MVNV: n = 9, 9.67 ± 1.41 years, ASD: n = 48, (ASD-V: n = 27, 10.55 ± 1.21 years, ASD-LI: n = 21, 10.67 ± 1.20 years) and TD: n = 27, 10.14 ± 1.38 years. Delayed MMF latencies were found bilaterally in ASD-MVNV compared to verbal ASD (both ASD-V and ASD-LI) and TD children. Delayed MMF responses were associated with diminished language and communication skills. Furthermore, whereas the TD children showed leftward lateralization of MMF amplitude, ASD-MVNV and verbal ASD (ASD-V and ASD-LI) showed abnormal rightward lateralization. Findings suggest delayed auditory discrimination processes and abnormal rightward laterality as objective markers of language/communication skills in both verbal and MVNV children who have ASD. Autism Res 2019, 12: 1225-1235. © 2019 International Society for Autism Research, Wiley Periodicals, Inc. LAY SUMMARY: Brain imaging showed abnormal auditory discrimination processes in minimally-verbal/non-verbal children (MVNV) who have autism spectrum disorder (ASD). Delays in auditory discrimination were associated with impaired language and communication skills. Findings sug-

gest these auditory neural measures may be objective markers of language and communication skills in both verbal and, previously-understudied, MVNV children who have ASD.

Keywords: autism spectrum disorder, language and communication skill, magnetoencephalography, minimally verbal/non-verbal children, vowel mismatch fields

Autism research: official journal of the International Society for Autism Research (2019), Vol. 12, No. 8 (31136103)

A Spectrotemporal Correlate of Language Impairment in Autism Spectrum Disorder (2019)

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ABSTRACT This study introduces an objective neurophysiological marker of language ability, the integral of event-related desynchronization in the 5-20 Hz band during 0.2-1 seconds post auditory stimulation with interleaved word/non-word tokens. This measure correlates with clinical assessment of language function in both ASD and neurotypical pediatric populations. The measure does not appear related to general cognitive ability nor autism symptom severity (beyond degree of language impairment). We suggest that this oscillatory brain activity indexes lexical search and thus increases with increased search in the mental lexicon. While specificity for language impairment in ASD remains to be determined, such an objective index has potential utility in low functioning individuals with ASD and young children during language acquisition.

Keywords: Language impairment, Lexical access, Magnetoencephalography (MEG), Oscillation

Journal of autism and developmental disorders (2019), Vol. 49, No. 8 (31069618)

Abnormal maturation of the resting-state peak alpha frequency in children with autism spectrum disorder (2020)

Edgar, J Christopher; Dipiero, Marissa; McBride, Emma; Green, Heather L; Berman, Jeffrey; Ku, Matthew; Liu, Song; Blaskey, Lisa; Kuschner, Emily; Airey, Megan; Ross, Judith L; Bloy, Luke; Kim, Mina; Koppers, Simon; Gaetz, William; Schultz, Robert T; Roberts, Timothy P L

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ABSTRACT Age-related changes in resting-state (RS) neural rhythms in typically developing children (TDC) but not children with autism spectrum disorder (ASD) suggest that RS measures may be of clinical use in ASD only for certain ages. The study examined this issue via assessing RS peak alpha frequency (PAF), a measure previous studies, have indicated as abnormal in ASD. RS magnetoencephalographic (MEG) data were obtained from 141 TDC (6.13-17.70 years) and 204 ASD (6.07-17.93 years). A source model with 15 regional sources projected the raw MEG surface data into brain source space. PAF was identified in each participant from the source showing the largest amplitude alpha activity (7-13 Hz). Given sex differences in PAF in TDC (females > males) and relatively few females in both groups, group comparisons were conducted examining only male TDC (N = 121) and ASD (N = 183). Regressions showed significant group slope differences, with an age-related increase in PAF in TDC (R[2] = 0.32) but not ASD (R[2] = 0.01). Analyses examining male children below or above 10-years-old (median split) indicated group effects only in the younger TDC (8.90 Hz) and ASD (9.84 Hz; Cohen's d = 1.05). In the older ASD, a higher nonverbal IQ was associated with a higher PAF. In the younger TDC, a faster speed of processing was associated with a higher PAF. PAF as a marker for ASD depends on age,

with a RS alpha marker of more interest in younger versus older children with ASD. Associations between PAF and cognitive ability were also found to be age and group specific.

Keywords: alpha, autism spectrum disorders, magnetoencephalography, maturation, resting-state

Human brain mapping (2019), Vol. 40, No. 11 (30977235)

Children with Autism Spectrum Disorder Demonstrate Regionally Specific Altered Resting-State Phase-Amplitude Coupling (2020)

Port, Russell G; Dipiero, Marissa A; Ku, Matthew; Liu, Song; Blaskey, Lisa; Kuschner, Emily S; Edgar, J Christopher; Roberts, Timothy P L; Berman, Jeffrey I

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ABSTRACT Studies suggest that individuals with autism spectrum disorder (ASD) exhibit altered electrophysiological alpha to gamma phase-amplitude coupling (PAC). Preliminary reports with small samples report conflicting findings regarding the directionality of the alpha to gamma PAC alterations in ASD. The present study examined resting-state activity throughout the brain in a relatively large sample of 119 children with ASD and 47 typically developing children. Children with ASD demonstrated regionally specific abnormalities in alpha to low-gamma PAC, with increased alpha to low-gamma PAC for a central midline source and decreased PAC at lateral sources. Group differences in local gamma-band power did not account for the regional group differences in alpha to low-gamma PAC. Moreover, local alpha power did not significantly modulate alpha to low-gamma PAC estimates. Finally, PAC estimates were correlated with Social Responsiveness Scale (SRS) indicating clinical relevance of the PAC metric. In conclusion, alpha to low-gamma PAC alterations in ASD demonstrate a heterogeneous spatial profile consistent with previous studies and were related to symptom severity.

Keywords: MEG, PAC, alpha, autism spectrum disorder, gamma, resting state

Brain connectivity (2019), Vol. 9, No. 5 (30900464)

Auditory evoked response delays in children with 47,XYY syndrome (2019)

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ABSTRACT 47,XYY syndrome (XYY) is a male sex chromosome disorder where individuals have an X chromosome and two copies of the Y chromosome. XYY is associated with a physical phenotype and carries increased risk of neurodevelopmental disorders such as autism spectrum disorder (ASD). Latencies of auditory evoked responses measured by magnetoencephalography have shown atypical prolongations in several neuropsychiatric and genetic disorders; specifically, delayed auditory responses have been observed in ASD. In this study, we investigated the associations of genotype and clinical phenotype with auditory processing. Whole cortex magnetoencephalography recorded during a passive auditory paradigm (500 Hz tones) was used to assess the auditory evoked response in three groups of male children: idiopathic ASD, typically developing, and XYY boys. Response waveforms were computed for left and right auditory cortex and latencies of the 50 ms (M50) and 100 ms (M100) components were determined. M50 latencies were significantly delayed compared with typically developing controls in children with ASD in the right hemisphere only, and in children with XYY in the left hemisphere only, irrespective of whether they met diagnostic criteria for ASD. Findings on the later M100 component trended in the same directions but did not attain significance, due to increased variance. Replicating previous findings, decreased M50 and M100 latencies with

age were observed bilaterally. Overall, while XYY shares an electrophysiological phenotype (delayed evoked response latency) with idiopathic ASD, the hemispheric differences warrant further investigation.

Neuroreport (2019), Vol. 30, No. 7 (30896674)

Neural gain control measured through cortical gamma oscillations is associated with sensory sensitivity (2020)

Orekhova, Elena V; Stroganova, Tatiana A; Schneiderman, Justin F; Lundström, Sebastian; Riaz, Bushra; Sarovic, Darko; Sysoeva, Olga V; Brant, Georg; Gillberg, Christopher; Hadjikhani, Nouchine

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ABSTRACT Gamma oscillations facilitate information processing by shaping the excitatory input/output of neuronal populations. Recent studies in humans and nonhuman primates have shown that strong excitatory drive to the visual cortex leads to suppression of induced gamma oscillations, which may reflect inhibitory-based gain control of network excitation. The efficiency of the gain control measured through gamma oscillations may in turn affect sensory sensitivity in everyday life. To test this prediction, we assessed the link between self-reported sensitivity and changes in magneto-encephalographic gamma oscillations as a function of motion velocity of high-contrast visual gratings. The induced gamma oscillations increased in frequency and decreased in power with increasing stimulation intensity. As expected, weaker suppression of the gamma response correlated with sensory hypersensitivity. Robustness of this result was confirmed by its replication in the two samples: neurotypical subjects and people with autism, who had generally elevated sensory sensitivity. We conclude that intensity-related suppression of gamma response is a promising biomarker of homeostatic control of the excitation-inhibition balance in the visual cortex.

Keywords: autism spectrum disorders, gamma oscillations, magneto-encephalography, response gain control, sensory sensitivity, visual motion

Human brain mapping (2019), Vol. 40, No. 5 (30549144)

Band-specific atypical functional connectivity pattern in childhood autism spectrum disorder (2017)

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OBJECTIVE Altered brain connectivity has been theorized as a key neural underpinning of autism spectrum disorder (ASD), but recent investigations have revealed conflicting patterns of connectivity, particularly hyperconnectivity and hypo-connectivity across age groups. The application of graph theory to neuroimaging data has become an effective approach for characterizing topographical patterns of large-scale functional networks. We used a graph approach to investigate alteration of functional networks in childhood ASD.

METHOD Magnetoencephalographic signals were quantified using graph-theoretic metrics with a phase lag index (PLI) for specific bands in 24 children with

autism spectrum disorder and 24 typically developing controls.

RESULTS No significant group difference of PLI was found. Regarding topological organization, enhanced and reduced small-worldness, representing the efficiency of information processing, were observed respectively in ASD children, particularly in the gamma band and delta band.

CONCLUSIONS Analyses revealed frequency-dependent atypical neural network topologies in ASD children.

SIGNIFICANCE Our findings underscore the recently proposed atypical neural network theory of ASD during childhood. Graph theory with PLI applied to magnetoencephalographic signals might be a useful approach for characterizing the frequency-specific neurophysiological bases of ASD.

Keywords: Autism spectrum disorder (ASD), Childhood, Functional network, Graph theory, Magnetoencephalography (MEG), Phase lag index (PLI)

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2017), Vol. 128, No. 8 (28622528)

Magnetoencephalographic Imaging of Auditory and Somatosensory Cortical Responses in Children with Autism and Sensory Processing Dysfunction

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ABSTRACT This study compared magnetoencephalographic (MEG) imaging-derived indices of auditory and somatosensory cortical processing in children aged 8-12 years with autism spectrum disorder (ASD; N = 18), those with sensory processing dysfunction (SPD; N = 13) who do not meet ASD criteria, and typically developing control (TDC; N = 19) participants. The magnitude of responses to both auditory and tactile stimulation was comparable across all three groups; however, the M200 latency response from the left auditory cortex was significantly delayed in the ASD group relative to both the TDC and SPD groups, whereas the somatosensory response of the ASD group was only delayed relative to TDC participants. The SPD group did not significantly differ from either group in terms of somatosensory latency, suggesting that participants with SPD may have an intermediate phenotype between ASD and TDC with regard to somatosensory processing. For the ASD group, correlation analyses indicated that the left M200 latency delay was significantly associated with performance on the WISC-IV Verbal Comprehension Index as well as the DSTP Acoustic-Linguistic index. Further, these cortical auditory response delays were not associated with somatosensory cortical response delays or cognitive processing speed in the ASD group, suggesting that auditory delays in ASD are domain specific rather than associated with generalized processing delays. The specificity of these auditory delays to the ASD group, in addition to their correlation with verbal abilities, suggests that auditory sensory dysfunction may be implicated in communication symptoms in ASD, motivating further research aimed at understanding the impact of sensory dysfunction on the developing brain.

Keywords: auditory evoked fields, autism spectrum disorders (ASD), communication, processing speed, sensory processing disorder, somatosensory evoked fields

Frontiers in human neuroscience (2017), Vol. 11 (28603492)

Disconnection from others in autism is more than just a feeling: whole-brain neural synchrony in adults during implicit processing of emotional faces (2017)

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BACKGROUND Socio-emotional difficulties in autism spectrum disorder (ASD) are thought to reflect impaired functional connectivity within the "social brain". Nonetheless, a whole-brain characterization of the fast responses in functional connectivity during implicit processing of emotional faces in adults with ASD is lacking.

METHODS The present study used magnetoencephalography to investigate early responses in functional connectivity, as measured by interregional phase synchronization, during implicit processing of angry, neutral and happy faces. The sample (n = 44) consisted of 22 young adults with ASD and 22 age- and sex-matched typically developed (TD) controls.

RESULTS Reduced phase-synchrony in the beta band around 300 ms emerged during processing of angry faces in the ASD compared to TD group, involving key areas of the social brain. In the same time window, desynchronization in the beta band in the amygdala was reduced in the ASD group across conditions.

CONCLUSIONS This is the first demonstration of atypical global and local synchrony patterns in the social brain in adults with ASD during implicit processing of emotional faces. The present results replicate and substantially extend previous findings on adolescents, highlighting that atypical brain synchrony during processing of socio-emotional stimuli is a hallmark of clinical sequelae in autism.

Keywords: Autism, Emotional faces, Functional connectivity, Magnetoencephalography, Social brain, Young adults

Molecular autism (2017), Vol. 8 (28316771)

Mismatch field latency, but not power, may mark a shared autistic and schizotypal trait phenotype (2018)

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ABSTRACT The auditory mismatch negativity (MMN), a preattentive processing potential, and its magnetic counterpart (MMF) are consistently reported as reduced in schizophrenia and autism spectrum disorders. This study investigates whether MMF characteristics differ between subclinically high and low scorers on the recently discovered shared autism and schizophrenia phenotype, Social Disorganisation. A total of 18 low (10 females) and 19 high (9 females) Social Disorganisation scorers underwent magnetoencephalography (MEG) during a MMF paradigm of 50ms standard (1000Hz, 85%) and 100ms duration deviant tones. MMF was measured from the strongest active magnetometer over the right and left hemispheres (consistent across groups) after 100ms. No differences in MMF power were found, however there was a significant delay in the MMF peak (p=0.007). The P3am (following the MMF) was significantly reduced across both hemispheres for the high Social Disorganisation group (p=0.025), there were no specific hemispheric differences in P3am power or latency. Right MMF peak latency increased with higher scores on the schizotypal subscales Odd Speech, Odd Behaviour and Constricted Affect. Findings suggest that MMF peak latency delay marks a convergence of the autism and schizophrenia spectra at a subclinical. These findings have significant implications for future research methodology, as well as clinical practice.

Keywords: Autism, Magnetoencephalography, Mismatch field, Mismatch negativity, Schizophrenia, Social Disorganisation

International journal of psychophysiology: official journal of the International Organization of Psychophysiology (2017), Vol. 116 (28235554)

Developmental changes in neuromagnetic rhythms and network synchrony in autism (2017)

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OBJECTIVE There is gathering consensus that altered connectivity is a hallmark of the autistic brain. This includes atypical neural oscillations and their coordination across brain regions, which are understood to mediate information processing and integration. It remains unclear whether and how connectivity in various neurophysiological frequency ranges develops atypically in autism spectrum disorder (ASD).

METHODS To address this in a cross-sectional sample, we recorded resting-state magnetoencephalography from 134 children and adolescents with and without ASD, and calculated resting spectral power and interregional synchrony (functional connectivity).

RESULTS Although no overall group differences were observed, significant alterations in linear and nonlinear age-related changes in resting oscillatory power and network synchrony were found. These differences were frequency- and region-specific and implicated brain systems thought to play a prominent role in ASD, such as the frontal cortex and cerebellum. We also found correlations between Autism Diagnostic Observation Schedule scores and the degree to which connectivity in cerebellar networks is "idiosyncratic" in an individual with autism.

INTERPRETATION We provide the first evidence that it is the curvatures of maturational changes in neurophysiological oscillations and synchrony, rather than disturbances in a particular direction, that characterize the brain function in individuals with ASD. Moreover, the patterns of idiosyncratic distortions of network synchrony relative to the group curve are associated with behavioral symptoms of ASD. Ann Neurol 2017;81:199-211.

Annals of neurology (2017), Vol. 81, No. 2 (27977875)

Bipolar Disorder

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)

Complexity analysis of spontaneous brain activity in mood disorders: A magnetoencephalography study of bipolar disorder and major depression (2019)

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BACKGROUND AND PURPOSE The lack of a biomarker for Bipolar Disorder (BD) causes problems in the differential diagnosis with other mood disorders such as major depression (MD), and misdiagnosis frequently

occurs. Bearing this in mind, we investigated non-linear magnetoencephalography (MEG) patterns in BD and MD.

METHODS Lempel-Ziv Complexity (LZC) was used to evaluate the resting-state MEG activity in a cross-sectional sample of 60 subjects, including 20 patients with MD, 16 patients with BD type-I, and 24 control (CON) subjects. Particular attention was paid to the role of age. The results were aggregated by scalp region.

RESULTS Overall, MD patients showed significantly higher LZC scores than BD patients and CONs. Linear regression analyses demonstrated distinct tendencies of complexity progression as a function of age, with BD patients showing a divergent tendency as compared with MD and CON groups. Logistic regressions confirmed such distinct relationship with age, which allowed the classification of diagnostic groups.

CONCLUSIONS The patterns of neural complexity in BD and MD showed not only quantitative differences in their non-linear MEG characteristics but also divergent trajectories of progression as a function of age. Moreover, neural complexity patterns in BD patients resembled those previously observed in schizophrenia, thus supporting preceding evidence of common neuropathological processes.

Keywords: Bipolar disorder, Lempel-Ziv Complexity, Magnetoencephalography, Mood disorders, Psychosis Continuum

Comprehensive psychiatry (2018), Vol. 84 (29734005)

Dissociable auditory mismatch response and connectivity patterns in adolescents with schizophrenia and adolescents with bipolar disorder with psychosis: A magnetoencephalography study (2018)

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BACKGROUND There is overlap between schizophrenia and bipolar disorder regarding genetic risk as well as neuropsychological and structural brain deficits. Finding common and distinct event-response potential (ERP) responses and connectivity patterns may offer potential biomarkers to distinguish the disorders.

OBJECTIVE To examine the neuronal auditory response elicited by a roving mismatch negativity (MMN) paradigm using magnetoencephalography (MEG).

PARTICIPANTS 15 Adolescents with schizophrenia (ASZ), 16 adolescents with bipolar disorder with psychosis (ABP), and 14 typically developing individuals (TD) METHODS: The data were analysed using time-series techniques and dynamic causal modelling (DCM).

OUTCOME MEASURES MEG difference wave (deviant - standard) at primary auditory (~90ms), MMN (~180ms) and long latency (~300ms).

RESULTS The amplitude of difference wave showed specific patterns at all latencies. Most notably, it was significantly reduced ABP compared to both controls and ASZ at early latencies. In contrast, the amplitude was significantly reduced in ASZ compared to both controls and ABP. The DCM analysis showed differential connectivity patterns in all three groups. Most notably, inter-hemispheric connections were strongly dominated by the right side in ASZ only.

CONCLUSIONS Dissociable patterns of the primary auditory response and MMN response indicate possible developmentally sensitive, but separate biomarkers for schizophrenia and bipolar disorder.

Keywords: Biomarker, Bipolar disorder, Connectivity, First episode, Mismatch negativity, Schizophrenia

Schizophrenia research (2018), Vol. 193 (28760539)

Brain Neoplasms

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

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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)

Disrupted network connectivity in pediatric brain tumor survivors is a signature of injury (2020)

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ABSTRACT Cognition is compromised in pediatric brain tumor survivors but the neurophysiological basis of this compromise remains unclear. We hypothesized that reduced neural synchronization across brain networks is involved. To test this, we evaluated group differences using a retrospective cohort comparison design between 24 pediatric brain tumor survivors [11.81 ± 3.27)] and 24 age matched healthy children [12.04 ± 3.28)] in functional connectivity within a cerebellar network to examine local effects of the tumor, a whole brain network to examine diffuse effects of treatment (i.e., chemotherapy and radiation), and across multiple intrinsic connectivity networks. Neural activity was recorded during magnetoencephalography scanning while participants were at rest and functional connectivity within networks was measured using the phase lag index. We corroborated our findings using a computational model representing the local tumor effects on neural synchrony. Compared to healthy children, pediatric brain tumor survivors show increased functional connectivity for theta and beta frequency bands within the cerebellar network and increased functional connectivity for the theta band within the whole brain network that again localized to the cerebellum. Computational modeling showed that increased synchrony in the theta bad is observed following local clustering as well as sparse interarea brain connectivity. We also observed increased functional connectivity for the alpha frequency band in the ventral attention network and decreased functional connectivity within the gamma frequency band in the motor network within paedatric brain tumor survivors versus healthy children. Notably, increased gamma functional connectivity within the motor network predicted decreased reaction time on behavioral tasks in pediatric brain tumor survivors. Disrupted network synchrony may be a signature of neurological injury and disease.

Keywords: CANTAB RRID:SCR_003001), Fieldtrip toolbox RRID:SCR_004849, brain tumor, computational modeling, functional connectivity, magnetoencephalography, network based statistics toolbox RRID:SCR_002454, neural network, pediatric

The Journal of comparative neurology (2019), Vol. 527, No. 17 (31125446)

Understanding cognitive functioning in glioma patients: The relevance of IDH-mutation status and functional connectivity (2019)

Derks, Jolanda; Kulik, Shanna; Wesseling, Pieter; Numan, Tianne; Hillebrand, Arjan; van Dellen, Edwin; de Witt Hamer, Philip C; Geurts, Jeroen J G; Reijneveld, Jaap C; Stam, Cornelis J; Klein, Martin; Douw, Linda

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INTRODUCTION Cognitive deficits occur frequently in diffuse glioma patients, but are limitedly understood. An important marker for survival in these patients is isocitrate dehydrogenase (IDH) mutation (IDH-mut). Patients with IDH-mut glioma have a better prognosis but more often suffer from epilepsy than patients with IDH-wildtype (IDH-wt) glioma, who are generally older and more often have cognitive deficits. We investigated whether global brain functional connectivity differs between patients with IDH-mut and IDH-wt glioma, and whether this measure reflects variations in cognitive functioning in these subpopulations beyond the associated differences in age and presence of epilepsy.

METHODS We recorded magnetoencephalography and tested cognitive functioning in 54 diffuse glioma patients (31 IDH-mut, 23 IDH-wt). Global functional connectivity between 78 atlas regions spanning the entire cortex was calculated in two frequency bands (theta and alpha). Group differences in global functional connectivity were tested, as was their association

with cognitive functioning, controlling for age, education, and presence of epilepsy.

RESULTS Patients with IDH-wt glioma had lower functional connectivity in the alpha band than patients with IDH-mut glioma ($p = 0.040$, corrected for age and presence of epilepsy). Lower alpha band functional connectivity was associated with poorer cognitive performance ($p < 0.034$), corrected for age, education, and presence of epilepsy.

CONCLUSION Global functional connectivity is lower in patients with IDH-wt diffuse glioma compared to patients with IDH-mut diffuse glioma. Moreover, having lower functional alpha connectivity relates to poorer cognitive performance in patients with diffuse glioma, regardless of age, education, and presence of epilepsy.

Keywords: cognition, diffuse glioma, isocitrate dehydrogenase, magnetoencephalography

Brain and behavior (2019), Vol. 9, No. 4 (30809977)

MEG imaging of recurrent gliomas reveals functional plasticity of hemispheric language specialization (2020)

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ABSTRACT In patients with gliomas, changes in hemispheric specialization for language determined by magnetoencephalography (MEG) were analyzed to elucidate the impact of treatment and tumor recurrence on language networks. Demonstration of reorganization of language networks in these patients has significant implications on the prevention of postoperative functional loss and recovery. Whole-brain activity during an auditory verb generation task was estimated from MEG recordings in a group of 73 patients with recurrent gliomas. Hemisphere of language dominance was estimated using the language laterality index (LI), a measure derived from the task. The initial scan was performed prior to resection; patients subsequently underwent surgery and adjuvant treatment. A second scan was performed upon recurrence prior to repeat resection. The relationship between the shift in LI between scans and demographics, anatomic location, pathology, and adjuvant treatment was analyzed. Laterality shifts were observed between scans; the median percent change was 29.1% across all patients. Laterality shift magnitude and relative direction were associated with the initial position of language dominance; patients with increased lateralization experienced greater shifts than those presenting more bilateral representation. A change in LI from left or right to bilateral (or vice versa) occurred in 23.3% of patients; complete switch occurred in 5.5% of patients. Patients with tumors within the language-dominant hemisphere experienced significantly greater shifts than those with contralateral tumors. The majority of patients with glioma experience shifts in language network organization over time which correlate with the relative position of language lateralization and tumor location.

Keywords: brain tumor, glioma, language dominance, language laterality index, language lateralization, magnetoencephalography, neurosurgery, recurrence, verb generation

Human brain mapping (2019), Vol. 40, No. 4 (30549134)

Histopathologic and Clinical Correlation of Aberrant Neuromagnetic Activities with Low to High Frequency of Gliomas (2019)

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OBJECTIVE To quantify the low- to high-frequency range of abnormal brain activities and assess the histopathologic and clinical correlation in patients with glioma.

METHODS Twenty-five patients with glioma and 20 healthy controls were examined with a magnetoencephalography (MEG) system. MEG data collected in 6 frequency bands, including 1-4 Hz, 4-8 Hz, 8-12 Hz, 12-30 Hz, 30-45 Hz, and 55-75 Hz, were analyzed by neuropathology to assess neuromagnetic signatures of glioma grade.

RESULTS Compared with controls, patients with glioma showed greatly altered brain activities in 4-8 Hz, 8-12 Hz, and 55-75 Hz. Magnetic source power of brain activities in 4-8 Hz and 55-75 Hz in patients with high-grade gliomas significantly differed from that in patients with low-grade gliomas. The magnitude of source power of brain activities in 4-8 Hz and 55-75 Hz had marked correlation with the grading of gliomas in histopathological analyses.

CONCLUSIONS The degree of neuromagnetic source abnormality is a potential biomarker for noninvasive assessment of glioma grade. Because MEG tests can be performed noninvasively and preoperatively, MEG may play an important role in clinical biopsies and surgical planning for patients with brain gliomas in the future.

Keywords: Accumulated source imaging, Brain activities, Glioma, Magnetoencephalography, Multiple frequency analysis

World neurosurgery (2019), Vol. 123 (30529596)

Cognitive functioning and functional brain networks in postoperative WHO grade I meningioma patients (2019)

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INTRODUCTION Meningioma patients often have subtle cognitive deficits that might be attributed to the tumor itself, to surgical treatment, or to the occurrence of seizures and their treatment. Magnetoencephalography (MEG) analysis of resting-state functional networks (RSNs) could help to understand the neurophysiological basis of cognitive impairment in these patients. We explored the correlation between RSN functional connectivity and topology of functional networks on the one hand, and cognition on the other hand in WHO grade I meningioma patients.

METHODS Twenty adult WHO grade I meningioma patients who had undergone tumor resection, as well as 20 healthy matched controls, were included. Neuropsychological assessment was done through a standardized test battery. MEG data were recorded, and projected to the anatomical space of the Automated Anatomical Labeling atlas. Functional connectivity (PLI), within the default mode network (DMN) and the bilateral frontoparietal networks were correlated to cognitive performance. Minimum spanning tree (MST) characteristics were correlated with cognitive functioning.

RESULTS Compared to healthy controls, meningioma patients had lower working memory capacity ($p = 0.037$). Within the patient group, lower working memory performance was associated with lower DMN connectivity and a lower maximum MST degree in the theta band (resp. $p = 0.044$ and $p = 0.003$).

CONCLUSIONS This study shows that cognitive functioning is correlated with functional connectivity in the default mode network and hub-pathology in WHO grade I meningioma patients. Future longitudinal studies are needed to corroborate these findings and to further investigate the pathophysiology of cognitive deficits and possible changes in functional brain networks in meningioma patients.

Keywords: Cognitive functioning, Functional connectivity, Magnetoencephalography, Meningioma, Minimum spanning tree, Resting-state networks

Journal of neuro-oncology (2018), Vol. 140, No. 3 (30219943)

Oscillatory brain activity associates with neuroligin-3 expression and predicts progression free survival in patients with diffuse glioma (2018)

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INTRODUCTION Diffuse gliomas have local and global effects on neurophysiological brain functioning, which are often seen as 'passive' consequences of the tumor. However, seminal preclinical work has shown a prominent role for neuronal activity in glioma growth: mediated by neuroligin-3 (NLGN3), increased neuronal activity causes faster glioma growth. It is unclear whether the same holds true in patients. Here, we investigate whether lower levels of oscillatory brain activity relate to lower NLGN3 expression and predict longer progression free survival (PFS) in diffuse glioma patients.

METHODS Twenty-four newly diagnosed patients with diffuse glioma underwent magnetoencephalography and subsequent tumor resection. Oscillatory brain activity was approximated by calculating broadband power (0.5-48 Hz) of the magnetoencephalography. NLGN3 expression in glioma tissue was semi-quantitatively assessed by immunohistochemistry. Peritumor and global oscillatory brain activity was then compared between different levels of NLGN3 expression with Kruskal-Wallis tests. Cox proportional hazards analyses were performed to estimate the predictive value of oscillatory brain activity for PFS.

RESULTS Patients with low expression of NLGN3 had lower levels of global oscillatory brain activity than patients with higher NLGN3 expression ($P < 0.001$). Moreover, lower peritumor (hazard ratio 2.17, $P = 0.008$) and global oscillatory brain activity (hazard ratio 2.10, $P = 0.008$) predicted longer PFS.

CONCLUSIONS Lower levels of peritumor and global oscillatory brain activity are related to lower NLGN3 expression and longer PFS, corroborating preclinical research. This study highlights the important interplay between macroscopically measured brain activity and glioma progression, and may lead to new therapeutic interventions in diffuse glioma patients.

Keywords: Glioma, Magnetoencephalography, NLGN3, Neurophysiology, Tumor progression

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Dynamic hub load predicts cognitive decline after resective neurosurgery (2018)

Carbo, Ellen W S; Hillebrand, Arjan; van Dellen, Edwin; Tewarie, Prejaas; de Witt Hamer, Philip C; Baayen, Johannes C; Klein, Martin; Geurts, Jeroen J G; Reijneveld, Jaap C; Stam, Cornelis J; Douw, Linda

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ABSTRACT Resective neurosurgery carries the risk of postoperative cognitive deterioration. The concept of 'hub (over)load', caused by (over)use of the most important brain regions, has been theoretically postulated in relation to symptomatology and neurological disease course, but lacks experimental confirmation. We investigated functional hub load and postsurgical cognitive deterioration in patients undergoing lesion resection. Patients (n = 28) underwent resting-state magnetoencephalography and neuropsychological assessments preoperatively and 1-year after lesion resection. We calculated stationary hub load score (SHub) indicating to what extent brain regions linked different subsystems; high SHub indicates larger processing pressure on hub regions. Dynamic hub load score (DHub) assessed its variability over time; low values, particularly in combination with high SHub values, indicate increased load, because of consistently high usage of hub regions. Hypothetically, increased SHub and decreased DHub relate to hub overload and thus poorer/deteriorating cognition. Between time points, deteriorating verbal memory performance correlated with decreasing upper alpha DHub. Moreover, preoperatively low DHub values accurately predicted declining verbal memory performance. In summary, dynamic hub load relates to cognitive functioning in patients undergoing lesion resection: postoperative cognitive decline can be tracked and even predicted using dynamic hub load, suggesting it may be used as a prognostic marker for tailored treatment planning.

Scientific reports (2017), Vol. 7 (28169349)

Central Alexia

How Does iReadMore Therapy Change the Reading Network of Patients with Central Alexia? (2020)

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ABSTRACT Central alexia (CA) is an acquired reading disorder co-occurring with a generalized language deficit (aphasia). The roles of perilesional and ipsilesional tissue in recovery from poststroke aphasia are unclear. We investigated the impact of reading training (using iReadMore, a therapy app) on the connections within and between the right and left hemisphere of the reading network of patients with CA. In patients with pure alexia, iReadMore increased feedback from left inferior frontal gyrus (IFG) region to the left occipital (OCC) region. We aimed to identify whether iReadMore therapy was effective through a similar mechanism in patients with CA. Participants with chronic poststroke CA (n = 23) completed 35 h of iReadMore training over 4 weeks. Reading accuracy for trained and untrained words was assessed before and after therapy. The neural response to reading trained and untrained words in the left and right OCC, ventral occipitotemporal, and IFG regions was examined using event-related magnetoencephalography. The training-related modulation in effective connectivity between regions was modeled at the group level with dynamic causal modeling. iReadMore training improved participants' reading accuracy by an average of 8.4% (range, -2.77 to 31.66) while accuracy for untrained words was stable. Training increased regional sensitivity in bilateral frontal and occipital regions, and strengthened feedforward connections within the left hemisphere. Our data suggest that iReadMore training in these patients modulates lower-order visual representations, as opposed to higher-order, more abstract representations, to improve word-reading accuracy.SIGNIFICANCE STATEMENT This is the first study to conduct a network-level analysis of therapy effects in participants with poststroke central alexia. When patients trained with iReadMore (a multimodal, behavioral, mass practice, computer-based therapy), reading accuracy improved by an average 8.4% on trained items. A network analysis of the magnetoencephalography data associated with this improvement revealed an increase in regional sensitivity in bilateral frontal and occipital regions and strengthening of feedforward connections within the left hemisphere. This indicates that in patients with CA iReadMore engages lower-order, intact resources within the left hemisphere (posterior to their lesion locations) to improve word reading. This provides a foundation for future research to investigate reading network modulation in different CA subtypes, or for sentence-level therapy.

Keywords: DCM, MEG, alexia, aphasia, reading, stroke

The Journal of neuroscience: the official journal of the Society for Neuroscience (2019), Vol. 39, No. 29 (31085605)

Chronic Disease

Gulf War illness (GWI) as a neuroimmune disease (2018)

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ABSTRACT Gulf War illness (GWI) is a chronic disease characterized by the involvement of several organs, including the brain (Christova et al., Exp Brain Res doi: 10.1007/s00221-017-5010-8 , 2017). In a previous study (Georgopoulos et al., J Neural Eng 4:349-355, 2015), we identified six protective alleles from Class II human leukocyte antigen (HLA) genes, and more recently, we investigated the brain correlates of this protection (James et al., EBioMedicine 13:72-79, 2016). Those and other studies (Israeli, Lupus, 21:190-194, 2012) suggested an involvement of the immune system in GWI. In a recent study (Engdahl et al., EBioMedicine doi: 10.1016/j.ebiom.2016.08.030 , 2016), we showed that the brain pattern of synchronous neural interactions (SNI; Georgopoulos et al., J Neural Eng 4:349-355, 2007) in GWI is distinctly different from that in healthy controls. Here we focused on the SNI itself, as a basic measure of neural communication (irrespective of specific connections) and compared it between GWI and seven other diseases that cover a broad spectrum of etiology and pathophysiology. Specifically, we sought to determine which, if any, of those diseases might resemble GWI SNI, overall and within the HLA protective domain, and thus gain further knowledge regarding the nature of GWI brain abnormality. We studied a total of 962 participants from a healthy control population (N = 583) and eight different diseases, including GWI (N = 40), schizophrenia (SZ; N = 21), Alzheimer's disease (AD; N = 66), posttraumatic stress disorder (PTSD; N = 159), major depressive disorder (MDD; N = 10), relapsing-remitting multiple sclerosis (RRMS; N = 43), Sjögren's syndrome (SS; N = 32), and rheumatoid arthritis (RA; N = 8). They all underwent a resting-state magnetoencephalographic (MEG) scan to calculate SNIs. Data were analyzed using analysis of covariance (ANCOVA) with disease as fixed factor, and sex and age as covariates. We found that GWI SNIs differed significantly from control SZ, AD, PTSD and MDD but not from RRMS, SS and RA. In addition, we compared GWI to RRMS, SS and RA with respect to SNIs of MEG sensor pairs that were related to the HLA alleles protective for GWI (James et al., EBioMedicine 13:72-79, 2016). We found that GWI SNIs did not differ significantly from any of these three diseases but they did so from control SZ, AD, PTSD and MDD. These findings indicate that (a) GWI brain synchronicity does not differ significantly from that of known immune-related diseases (RRMS, SS, RA), and (b) that this SNI similarity is present within the HLA-related SNIs. In contrast, GWI SNIs differed significantly from those of the other diseases. We conclude that altered brain communication in GWI likely reflects immune-related processes, as postulated previously (James et al., EBioMedicine 13:72-79, 2016). By extension, these findings also indicate that functional brain abnormalities in RRMS, SS and RA might be, in part, due to lack of protective HLA alleles as documented for GWI (Georgopoulos et al., EBioMedicine 3:79-85, 2015).

Keywords: Alzheimer's disease, Gulf War illness (GWI), Human leukocyte antigen (HLA), Magnetoencephalography, Major depressive disorder, Posttraumatic stress disorder, Relapsing–remitting multiple sclerosis, Rheumatoid arthritis, Schizophrenia, Sjögren's syndrome, Veterans

Experimental brain research (2017), Vol. 235, No. 10 (28762055)

Dementia

A Graph Gaussian Embedding Method for Predicting Alzheimer's Disease Progression With MEG Brain Networks (2021)

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ABSTRACT Characterizing the subtle changes of functional brain networks associated with the pathological cascade of Alzheimer's disease (AD) is important for early diagnosis and prediction of disease progression prior to clinical symptoms. We developed a new deep learning method, termed multiple graph Gaussian embedding model (MG2G), which can learn highly informative network features by mapping high-dimensional resting-state brain networks into a low-dimensional latent space. These latent distribution-based embeddings enable a quantitative characterization of subtle and heterogeneous brain connectivity patterns at different regions, and can be used as input to traditional classifiers for various downstream graph analytic tasks, such as AD early stage prediction, and statistical evaluation of between-group significant alterations across brain regions. We used MG2G to detect the intrinsic latent dimensionality of MEG brain networks, predict the progression of patients with mild cognitive impairment (MCI) to AD, and identify brain regions with network alterations related to MCI.

IEEE transactions on bio-medical engineering (2021), Vol. 68, No. 5 (33400645)

Alterations in resting-state network dynamics along the Alzheimer's disease continuum (2021)

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 corre-

lated 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.

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Permutation Entropy and Statistical Complexity in Mild Cognitive Impairment and Alzheimer's Disease: An Analysis Based on Frequency Bands

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ABSTRACT We present one of the first applications of Permutation Entropy (PE) and Statistical Complexity (SC) (measured as the product of PE and Jensen-Shanon Divergence) on Magnetoencephalography (MEG) recordings of 46 subjects suffering from Mild Cognitive Impairment (MCI), 17 individuals diagnosed with Alzheimer's Disease (AD) and 48 healthy controls. We studied the differences in PE and SC in broadband signals and their decomposition into frequency bands (δ , θ , α and β), considering two modalities: (i) raw time series obtained from the magnetometers and (ii) a reconstruction into cortical sources or regions of interest (ROIs). We conducted our analyses at three levels: (i) at the group level we compared SC in each frequency band and modality between groups; (ii) at the individual level we compared how the [PE, SC] plane differs in each modality; and (iii) at the local level we explored differences in scalp and cortical space. We recovered classical results that considered only broadband signals and found a nontrivial pattern of alterations in each frequency band, showing that SC does not necessarily decrease in AD or MCI.

Keywords: Alzheimer's disease, frequency bands, mild cognitive impairment, permutation entropy, regions of interest, statistical complexity

Entropy (Basel, Switzerland) (2020), Vol. 22, No. 1 (33285891)

High-dimensional brain-wide functional connectivity mapping in magnetoencephalography (2021)

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BACKGROUND Brain functional connectivity (FC) analyses based on magneto/electroencephalography (M/EEG) signals have yet to exploit the intrinsic high-dimensional information. Typically, these analyses are constrained to regions of interest to avoid the curse of dimensionality, with the latter leading to conservative hypothesis testing.

NEW METHOD We removed such constraint by estimating high-dimensional source-based M/EEG-FC using cluster-permutation statistic (CPS) and demonstrated the feasibility of this approach by identifying resting-state changes in mild cognitive impairment (MCI), a prodromal stage of Alzheimer's disease. Particularly, we proposed a unified framework for CPS analysis together with a novel neighbourhood measure to estimate more compact and neurophysiological plausible neural communication. As clusters could more confidently reveal interregional communication, we proposed and tested a cluster-strength index to demonstrate other advantages of CPS analysis.

RESULTS We found clusters of increased communication or hypersynchronization in MCI compared to healthy controls in delta (1-4 Hz) and higher-theta (6-8 Hz) bands oscillations. These mainly consisted of interactions between occipitofrontal and occipitotemporal regions in the left hemisphere, which may be critically affected in the early stages of Alzheimer's disease.

CONCLUSIONS Our approach could be important to create high-resolution FC maps from neuroimaging studies in general, allowing the multimodal analysis of neural communication across multiple spatial scales. Particularly, FC clusters more robustly represent the interregional communication by identifying dense bundles of connections that are less sensitive to inter-individual anatomical and functional variability. Overall, this approach could help to better understand neural information processing in healthy and disease conditions as needed for developing biomarker research.

Keywords: Alzheimer's disease, Cluster permutation statistics, EEG and MEG biomarkers, Functional connectivity, Multiple comparison correction, Nonparametric statistics

Journal of neuroscience methods (2021), Vol. 348 (33181166)

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)

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.

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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.

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Dysfunction of Inferior Parietal Lobule During Sensory Gating in Patients With Amnestic Mild Cognitive Impairment

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ABSTRACT Patients with amnestic mild cognitive impairment (aMCI) demonstrate significant cognitive deficits, especially in the memory aspect. The memory deficiency might be attributed to the difficulties in the inhibitory function to suppress redundant stimuli. Sensory gating (SG) refers to the attenuation of neural responses to the second identical stimulus in a paired-click paradigm, in which auditory stimuli are delivered in pairs with inter-stimulus intervals (ISI) of 500 ms and inter-pair intervals of 6-8 s. It is considered as an electrophysiological signal to reflect the brain's automatic response to gate out repetitive sensory inputs. However, there has been no study systematically investigating SG function in aMCI patients. Thus, the present study used magnetoencephalography (MEG) to record neuromagnetic responses to a paired-click paradigm in 23 healthy controls (HC) and 26 aMCI patients. The Stimulus 2/Stimulus 1 (S2/S1) amplitude ratio was used to represent the SG function. Compared to HC, aMCI patients showed M50 SG deficits in the left inferior frontal gyrus (IFG) and right inferior parietal lobule (IPL). M100 SG defects were also observed in the right IPL. Based on the ROIs showing significant between-group SG differences, we found that a more deficient M50 SG function in the right IPL was associated with poorer performance in the immediate recall of Logic Memory (LM), Chinese Version Verbal Learning Test (CVVLT) and Digit Span Backward (DSB) Test. Furthermore, the M50 SG ratios of the right IPL together with the neuropsychological performance of LM and CVVLT demonstrated very good accuracy in the discrimination of aMCI from HC. In conclusion, compared to HC, aMCI patients showed a significant SG deficit in the right IPL, which was correlated with the auditory short-term memory function. We suggest the combination of SG in the right IPL, LM and CVVLT to be sensitive indicators to differentiate aMCI patients from HC.

Keywords: aging, inhibitory control, magnetoencephalography (MEG), mild cognitive impairment, sensory gating

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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)

Hypersynchronization in mild cognitive impairment: the 'X' model (2020)

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ABSTRACT Hypersynchronization has been proposed as a synaptic dysfunction biomarker in the Alzheimer's disease continuum, reflecting the alteration of the excitation/inhibition balance. While animal models have verified this idea extensively, there is still no clear evidence in humans. Here we test this hypothesis, evaluating the risk of conversion from mild cognitive impairment (MCI) to Alzheimer's disease in a longitudinal study. We compared the functional resting state eyes-closed magnetoencephalographic networks of 54 patients with MCI who were followed-up every 6 months. According to their clinical outcome, they were split into: (i) the 'progressive' MCI (n = 27) group; and (ii) the 'stable' MCI group (n = 27). They did not differ in gender or educational level. For all participants, two magnetoencephalographic recordings were acquired. Functional connectivity was evaluated using the phase locking value. To extract the functional connectivity network with significant changes between both magnetoencephalographic recordings, we evaluated the functional connectivity ratio, defined as functional connectivity post-/pre-condition, in a network-based statistical model with an ANCOVA test with age as covariate. Two significant networks were found in the theta and beta bands, involving fronto-temporal and fronto-occipital connections, and showing a diminished functional connectivity ratio in the progressive MCI group. These topologies were then evaluated at each condition showing that at baseline, patients with progressive MCI showed higher synchronization than patients with stable MCI, while in the post-condition this pattern was reversed. These results may be influenced by two main factors in the post-condition: the increased synchrony in the stable MCI patients and the network failure in the progressive MCI patients. These findings may be explained as an 'X' form model where the hypersynchrony predicts conversion, leading subsequently to a network breakdown in progressive MCI. Patients with stable MCI showed an opposite phenomenon, which could indicate that they were a step beyond in the Alzheimer's disease continuum. This model would be able to predict the risk for the conversion to dementia in MCI patients.

Keywords: classification, functional connectivity, longitudinal study, magnetoencephalography, stable and progressive mild cognitive impairment

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Spatiotemporal Oscillatory Patterns During Working Memory Maintenance in Mild Cognitive Impairment and Subjective Cognitive Decline (2020)

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ABSTRACT Working memory (WM) is a crucial cognitive process and its disruption is among the earliest symptoms of Alzheimer's disease. While alterations of the neuronal processes underlying WM have been evidenced in mild cognitive impairment (MCI), scarce literature is available in subjective cognitive decline (SCD). We used magnetoencephalography during a WM task performed by MCI (n = 45), SCD (n = 49) and healthy elders (n = 49) to examine group differences during the maintenance period (0-4000ms). Data were analyzed using time-frequency analysis and significant oscillatory differences were localized at the source level. Our results indicated significant differences between groups, mainly during the early maintenance (250-1250ms) in the theta, alpha and beta bands and in the late maintenance (2750-3750ms) in the theta band. MCI showed lower local synchronization in fronto-temporal cortical regions in the early theta-alpha window relative to controls (p = 2 × 10-03) and SCD (p = 4 × 10-03), and in the late theta window relative to controls (p = 1 × 1003) and SCD (p = 0.01). Early theta-alpha power was significantly correlated with memory scores (rho = 0.24,p = 0.02) and late theta power was correlated with task performance (rho = 0.24,p = 0.03) and functional activity scores (rho = -0.23,p = 0.02). In the early beta window, MCI showed reduced power in temporo-posterior regions relative to controls (p = 3 × 10-03) and SCD (p = 0.02). Our results may suggest that these alterations would reflect that memory-related networks are damaged.

Keywords: Alzheimer's disease (AD), Induced oscillatory activity, magnetoencephalography (MEG), mild cognitive impairment (MCI), subjective cognitive decline (SCD), working memory (WM)

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Aberrant MEG multi-frequency phase temporal synchronization predicts conversion from mild cognitive impairment-to-Alzheimer's disease (2020)

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ABSTRACT Many neuroimaging studies focus on a frequency-specific or a multi-frequency network analysis showing that functional brain networks are disrupted in patients with Alzheimer's disease (AD). Although those studies enriched our knowledge of the impact of AD in brain's functionality, our goal is to test the effectiveness of combining neuroimaging with network neuroscience to predict with high accuracy subjects with mild cognitive impairment (MCI) that will convert to AD. In this study, eyes-closed resting-state magnetoencephalography (MEG) recordings from 27 stable MCI (sMCI) and 27 progressive MCI (pMCI) from two scan sessions (baseline and follow-up after approximately 3 years) were projected via beamforming onto an atlas-based set of regions of interest (ROIs). Dynamic functional connectivity networks were constructed independently for the five classical frequency bands while a multivariate phase-based coupling metric was adopted. Thus, computing the distance between the fluctuation of functional strength of every pair of ROIs between the two conditions with dynamic time wrapping (DTW), a large set of features was extracted. A machine learning algorithm revealed 30 DTW-based features in the five frequency bands that can distinguish the sMCI from pMCI with absolute accuracy (100%). Further analysis of the selected links revealed that most of the connected ROIs were part of the default mode network (DMN), the cingulo-opercular (CO), the fronto-parietal and the sensorimotor network. Overall, our dynamic network multi-frequency analysis approach provides an effective framework of constructing a sensitive MEG-based connectome biomarker for the prediction of conversion from MCI to Alzheimer's disease.

Keywords: Connectomic biomarker, Conversion, Dynamic functional connectivity analysis, Magnetoencephalography, Mild cognitive impairment, Source reconstruction

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Neuropsychological and neurophysiological characterization of mild cognitive impairment and Alzheimer's disease in Down syndrome (2020)

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ABSTRACT Down syndrome (DS) has been considered a unique model for the investigation of Alzheimer's disease (AD) but intermediate stages in the continuum are poorly defined. Considering this, we investigated the neurophysiological (i.e., magnetoencephalography [MEG]) and neuropsychological patterns of mild cognitive impairment (MCI) and AD in middle-aged adults with DS. The sample was composed of four groups:

Control-DS (n = 14, mean age 44.64 ± 3.30 years), MCI-DS (n = 14, 51.64 ± 3.95 years), AD-DS (n = 13, 53.54 ± 6.58 years), and Control-no-DS (healthy controls, n = 14, 45.21 ± 4.39 years). DS individuals were studied with neuropsychological tests and MEG, whereas the Control-no-DS group completed only the MEG session. Our results showed that the AD-DS group exhibited a significantly poorer performance as compared with the Control-DS group in all tests. Furthermore, this effect was crucially evident in AD-DS individuals when compared with the MCI-DS group in verbal and working memory abilities. In the neurophysiological domain, the Control-DS group showed a widespread increase of theta activity when compared with the Control-no-DS group. With disease progression, this increased theta was substituted by an augmented delta, accompanied with a reduction of alpha activity. Such spectral pattern-specifically observed in occipital, posterior temporal, cuneus, and precuneus regions-correlated with the performance in cognitive tests. This is the first MEG study in the field incorporating both neuropsychological and neurophysiological information, and demonstrating that this combination of markers is sensitive enough to characterize different stages along the AD continuum in DS.

Keywords: Alzheimer's disease, Down syndrome, Magnetoencephalographic source analysis, Magnetoencephalography, Mild cognitive impairment, Neuropsychological performance

Neurobiology of aging (2019), Vol. 84 (31518951)

Biomagnetic biomarkers for dementia: A pilot multicentre study with a recommended methodological framework for magnetoencephalography

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INTRODUCTION An increasing number of studies are using magnetoencephalography (MEG) to study dementia. Here we define a common methodological framework for MEG resting-state acquisition and analysis to facilitate the pooling of data from different sites.

METHODS Two groups of patients with mild cognitive impairment (MCI, n = 84) and healthy controls (n = 84) were combined from three sites, and site and group differences inspected in terms of power spectra and functional connectivity. Classification accuracy for MCI versus controls was compared across three different types of MEG analyses, and compared with classification based on structural MRI.

RESULTS The spectral analyses confirmed frequency-specific differences in patients with MCI, both in power and connectivity patterns, with highest classification accuracy from connectivity. Critically, site acquisition differences did not dominate the results.

DISCUSSION This work provides detailed protocols and analyses that are sensitive to cognitive impairment, and that will enable standardized data sharing to facilitate large-scale collaborative projects.

Keywords: Functional connectivity, Harmonization, Magnetoencephalography, Mild cognitive impairment, Multi-site, Spectral analysis

Alzheimer's & dementia (Amsterdam, Netherlands) (2019), Vol. 11 (31431918)

Electrophysiological brain signatures for the classification of subjective cognitive decline: towards an individual detection in the preclinical stages of dementia (2020)

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BACKGROUND Alzheimer's disease (AD) prevalence is rapidly growing as worldwide populations grow older. Available treatments have failed to slow down disease progression, thus increasing research focus towards early or preclinical stages of the disease. Subjective cognitive decline (SCD) is known to increase the risk of developing AD and several other negative outcomes. However, it is still very scarcely characterized and there is no neurophysiological study devoted to its individual classification which could improve targeted sample recruitment for clinical trials.

METHODS Two hundred fifty-two older adults (70 healthy controls, 91 SCD, and 91 MCI) underwent a magnetoencephalography scan. Alpha relative power in the source space was employed to train a LASSO classifier and applied to distinguish between healthy controls and SCD. Moreover, MCI participants were used to further validate the previously trained algorithm.

RESULTS The classifier was significantly associated to SCD with an AUC of 0.81 in the whole sample. After randomly splitting the sample in 2/3 for discovery and 1/3 for validation, the newly trained classifier was also able to correctly classify SCD individuals with an AUC of 0.75 in the validation sample. The regions selected by the algorithm included medial frontal, temporal, and occipital areas. The algorithm trained to select SCD individuals was also significantly associated to MCI diagnostic.

CONCLUSIONS According to our results, magnetoencephalography could be a useful tool for distinguishing individuals with SCD and healthy older adults without cognitive concerns. Furthermore, our classifier showed good external validity, being not only successful for an unseen SCD sample, but also in a different population with MCI cases. This supports its utility in the context of preclinical dementia. These findings highlight the potential applications of electrophysiological techniques to improve sample recruitment at the individual level in the context of clinical trials.

Keywords: Alpha band, Alzheimer's disease, Magnetoencephalography, Neuroimaging, Subjective cognitive decline

Alzheimer's research & therapy (2019), Vol. 11, No. 1 (31151467)

Characterizing the fluctuations of dynamic resting-state electrophysiological functional connectivity: reduced neuronal coupling variability in mild cognitive impairment and dementia due to Alzheimer's disease (2020)

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OBJECTIVE The characterization of brain functional connectivity is a helpful tool in the study of the neuronal substrates and mechanisms that are altered in Azheimer's disease (AD) and mild cognitive impairment (MCI). Recently, there has been a shift towards the characterization of dynamic functional connectivity (dFC), discarding the assumption of connectivity stationarity during the resting-state. The majority of these studies have been performed with functional magnetic resonance imaging recordings, with only a small subset being based on magnetoencephalography/electroencephalography (MEG/EEG). However, only these modalities enable the characterization of potentially fast brain dynamics, which is mandatory for an accurate understanding of the transmission and processing of neuronal information. The aim of this study was to characterize the dFC of resting-state EEG activity in AD and MCI.

APPROACH Three measures: the phase lag index (PLI), leakage-corrected magnitude squared coherence (MSCOH) and leakage-corrected amplitude envelope correlation (AEC) were computed for 45 patients with

dementia due to AD, 51 subjects with MCI due to AD and 36 cognitively healthy controls. All measures were estimated in epochs of 60 s using a sliding window approach. An epoch length of 15 s was used to provide reliable results. We tested whether the observed PLI, MSCOH and AEC fluctuations reflected actual variations in functional connectivity, as well as whether between-group differences could be found.

MAIN RESULTS We found dFC using PLI, MSCOH and AEC, with AEC having the highest number of statistically significant connections, followed by MSCOH and PLI. Furthermore, a significant reduction in AEC dFC for patients with AD compared to controls was found in the alpha (8-13 Hz) and beta-1 (13-30 Hz) bands.

SIGNIFICANCE Our results suggest that patients with AD (and MCI subjects to a lesser degree) show less variation in neuronal connectivity during resting-state, supporting the notion that dFC can be found at the EEG time scale and is abnormal in the MCI-AD continuum. Measures of dFC have the potential of being used as biomarkers of AD. Moreover, they could also suggest that AD resting-state networks may operate at a state of low firing activity induced by the observed reduction in coupling strength. Furthermore, the statistically significant correlation between dFC and relative power in the beta-1 band could be related to pathologically high levels of neural activity inducing a loss of dFC. These findings show that the stability of neuronal coupling is affected in AD and MCI.

Journal of neural engineering (2019), Vol. 16, No. 5 (31112938)

Oscillatory hyperactivity and hyperconnectivity in young APOE- 4 carriers and hypoconnectivity in Alzheimer's disease (2020)

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ABSTRACT We studied resting-state oscillatory connectivity using magnetoencephalography in healthy young humans (N = 183) genotyped for APOE- 4, the greatest genetic risk for Alzheimer's disease (AD). Connectivity across frequencies, but most prevalent in alpha/beta, was increased in APOE- 4 in a set of mostly right-hemisphere connections, including lateral parietal and precuneus regions of the Default Mode Network. Similar regions also demonstrated hyperactivity, but only in gamma (40-160 Hz). In a separate study of AD patients, hypoconnectivity was seen in an extended bilateral network that partially overlapped with the hyperconnected regions seen in young APOE- 4 carriers. Using machine-learning, AD patients could be distinguished from elderly controls with reasonable sensitivity and specificity, while young APOE-e4 carriers could also be distinguished from their controls with above chance performance. These results support theories of initial hyperconnectivity driving eventual profound disconnection in AD and suggest that this is present decades before the onset of AD symptomology.

Keywords: APOE- 4, Alzheimer's disease, functional connectivity, human, neural oscillations, neuroscience, parietal cortex

eLife (2019), Vol. 8 (31038453)

Spontaneous oscillatory markers of cognitive status in two forms of dementia (2020)

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ABSTRACT Abnormal oscillatory brain activity in dementia may indicate incipient neuronal/synaptic dysfunction, rather than frank structural atrophy. Leveraging a potential link between the degree of abnormal oscillatory activity and cognitive symptom severity, one could localize brain regions in a diseased but pre-atrophic state, which may be more amenable to interventions. In the current study, we evaluated the relationships among cognitive deficits, regional volumetric changes, and resting-state magnetoencephalography abnormalities in patients with mild cognitive impairment (MCI; N = 10; age: 75.9 ± 7.3) or primary progressive aphasia (PPA; N = 12; 69.7 ± 8.0), and compared them to normal aging [young (N = 18; 24.6 ± 3.5), older controls (N = 24; 67.2 ± 9.7]. Whole-brain source-level resting-state estimates of relative oscillatory power in the delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (15-30 Hz) bands were combined with gray matter volumes and cognitive scores to examine between-group differences and brain-behavior correlations. Language and executive function (EF) abilities were impaired in patients with PPA, while episodic memory was impaired in MCI. Widespread oscillatory speeding and volumetric shrinkage was associated with normal aging, whereas the trajectory in PPA indicated widespread oscillatory slowing with additional volumetric reductions. Increases in delta and decreases in alpha power uniquely predicted group membership to PPA. Beyond volumetric reductions, more delta predicted poorer memory. In patients with MCI, no consistent group difference among oscillatory measures was found. The contributions of delta/alpha power on memory abilities were larger than volumetric differences. Spontaneous oscillatory abnormalities in association with cognitive symptom severity can serve as a marker of neuronal dysfunction in dementia, providing targets for promising treatments.

Keywords: dementia, magnetoencephalography, mild cognitive impairment, normal aging, primary progressive aphasia, resting-state

Human brain mapping (2019), Vol. 40, No. 5 (30421472)

Neural dynamics of selective attention deficits in HIV-associated neurocognitive disorder (2019)

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OBJECTIVE To identify the neural markers of attention dysfunction in patients with HIV-associated neurocognitive disorder (HAND).

METHODS Sixty participants, including 40 HIV-infected adults (half with HAND) and 20 demographically matched controls performed a visual selective attention task while undergoing high-density magnetoencephalography. Neuronal activity related to selective attention processing was quantified and compared across the 3 groups, and correlated with neuropsychological measures of attention and executive function. Spontaneous neural activity was also extracted from these attention-related cortical areas and examined with respect to HAND status.

RESULTS HIV-infected participants with and without HAND exhibited behavioral selective attention deficits on the magnetoencephalography task, as indicated by an increased flanker effect. Neuronal measures of flanker interference activity in the alpha and theta

range revealed differential dynamics in attention-related brain areas across the 3 groups, especially in those with HAND. In addition, theta range flanker interference activity in the left inferior frontal and dorsolateral prefrontal cortex was associated with executive function and attention composite scores, respectively. Progressively stronger spontaneous alpha and theta activity was also found in unimpaired HIV-infected and HAND participants relative to controls across brain regions implicated in different components of attention processing.

CONCLUSIONS Behavioral and neuronal metrics of selective attention performance distinguish participants with HAND from controls and unimpaired HIV-infected participants. These metrics, along with measures of local spontaneous neural activity, may hold promise as early markers of cognitive decline in participants with HIV infection and be useful prognostic indicators for HAND.

Neurology (2018), Vol. 91, No. 20 (30333162)

Neurophysiological signatures of Alzheimer's disease and frontotemporal lobar degeneration: pathology versus phenotype (2019)

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ABSTRACT The disruption of brain networks is characteristic of neurodegenerative dementias. However, it is controversial whether changes in connectivity reflect only the functional anatomy of disease, with selective vulnerability of brain networks, or the specific neurophysiological consequences of different neuropathologies within brain networks. We proposed that the oscillatory dynamics of cortical circuits reflect the tuning of local neural interactions, such that different pathologies are selective in their impact on the frequency spectrum of oscillations, whereas clinical syndromes reflect the anatomical distribution of pathology and physiological change. To test this hypothesis, we used magnetoencephalography from five patient groups, representing dissociated pathological subtypes and distributions across frontal, parietal and temporal lobes: amnestic Alzheimer's disease, posterior cortical atrophy, and three syndromes associated with frontotemporal lobar degeneration. We measured effective connectivity with graph theory-based measures of local efficiency, using partial directed coherence between sensors. As expected, each disease caused large-scale changes of neurophysiological brain networks, with reductions in local efficiency compared to controls. Critically however, the frequency range of altered connectivity was consistent across clinical syndromes that shared a likely underlying pathology, whilst the localization of changes differed between clinical syndromes. Multivariate pattern analysis of the frequency-specific topographies of local efficiency separated the disorders from each other and from controls (accuracy 62% to 100%, according to the groups' differences in likely pathology and clinical syndrome). The data indicate that magnetoencephalography has the potential to reveal specific changes in neurophysiology resulting from neurodegenerative disease. Our findings confirm that while clinical syndromes have characteristic anatomical patterns of abnormal connectivity that may be identified with other methods like structural brain imaging, the different mechanisms of neurodegeneration also cause characteristic spectral signatures of physiological coupling that are not accessible with structural imaging nor confounded by the neurovascular signalling of functional MRI. We suggest that these spectral characteristics of altered connectivity are the result of differential disruption of neuronal microstructure and synaptic physiology by Alzheimer's disease versus frontotemporal lobar degeneration.

Brain: a journal of neurology (2018), Vol. 141, No. 8 (30060017)

How to Build a Functional Connectomic Biomarker for Mild Cognitive Impairment From Source Reconstructed MEG Resting-State Activity: The Combination of ROI Representation and Connectivity Estimator Matters

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ABSTRACT Our work aimed to demonstrate the combination of machine learning and graph theory for the designing of a connectomic biomarker for mild cognitive impairment (MCI) subjects using eyes-closed neuromagnetic recordings. The whole analysis based on source-reconstructed neuromagnetic activity. As ROI representation, we employed the principal component analysis (PCA) and centroid approaches. As representative bi-variate connectivity estimators for the estimation of intra and cross-frequency interactions, we adopted the phase locking value (PLV), the imaginary part (iPLV) and the correlation of the envelope (CorrEnv). Both intra and cross-frequency interactions (CFC) have been estimated with the three connectivity estimators within the seven frequency bands (intra-frequency) and in pairs (CFC), correspondingly. We demonstrated how different versions of functional connectivity graphs single-layer (SL-FCG) and multi-layer (ML-FCG) can give us a different view of the functional interactions across the brain areas. Finally, we applied machine learning techniques with main scope to build a reliable connectomic biomarker by analyzing both SL-FCG and ML-FCG in two different options: as a whole unit using a tensorial extraction algorithm and as single pair-wise coupling estimations. We concluded that edge-weighed feature selection strategy outperformed the tensorial treatment of SL-FCG and ML-FCG. The highest classification performance was obtained with the centroid ROI representation and edge-weighted analysis of the SL-FCG reaching the 98% for the CorrEnv in α1:α2 and 94% for the iPLV in α2. Classification performance based on the multi-layer participation coefficient, a multiplexity index reached 52% for iPLV and 52% for CorrEnv. Selected functional connections that build the multivariate connectomic biomarker in the edge-weighted scenario are located in default-mode, fronto-parietal, and cingulo-opercular network. Our analysis supports the notion of analyzing FCG simultaneously in intra and cross-frequency whole brain interactions with various connectivity estimators in beamformed recordings.

Keywords: connectome data analysis, connectomic biomarker, cross-frequency-coupling, intrinsic coupling modes, magnetoencephalography, mild cognitive impairment, multiplexity, virtual source activity

Frontiers in neuroscience (2018), Vol. 12 (29910704)

Functional changes in the cortical semantic network in amnestic mild cognitive impairment (2019)

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OBJECTIVE Semantic memory impairment has been documented in individuals with amnestic Mild cognitive impairment (aMCI), who are at risk of developing Alzheimer's disease (AD), yet little is known about the neural basis of this breakdown. The aim of this study was to investigate the brain mechanisms associated with semantic performance in aMCI patients.

METHOD A group of aMCI patients and a group of healthy controls carried out a semantic categorization task while their brain activity was recorded using magnetoencephalography (MEG). During the task, participants were shown famous faces and had to determine whether each famous person matched a given occupation. The main hypotheses were that (a)

semantic processing should be compromised for aMCI patients, and (b) these deficits should be associated with cortical dysfunctions within specific areas of the semantic network.

RESULTS Behavioral results showed that aMCI participants were significantly slower and less accurate than controls at the semantic task. Additionally, relative to controls, a significant pattern of hyperactivation was found in the aMCI group within specific regions of the extended semantic network, including the right anterior temporal lobe (ATL) and fusiform gyrus.

CONCLUSIONS Abnormal functional activation within key areas of the semantic network suggests that it is compromised early in the disease process. Moreover, this pattern of right ATL and fusiform gyrus hyperactivation was positively associated with gray matter integrity in specific areas, but was not associated with any pattern of atrophy, suggesting that this pattern of hyperactivation may precede structural alteration of the semantic network in aMCI. (PsycINFO Database Record

Neuropsychology (2018), Vol. 32, No. 4 (29809032)

Electromagnetic signatures of the preclinical and prodromal stages of Alzheimer's disease (2019)

Nakamura, Akinori; Cuesta, Pablo; Fernández, Alberto; Arahata, Yutaka; Iwata, Kaori; Kuratsubo, Izumi; Bundo, Masahiko; Hattori, Hideyuki; Sakurai, Takashi; Fukuda, Koji; Washimi, Yukihiko; Endo, Hidetoshi; Takeda, Akinori; Diers, Kersten; Bajo, Ricardo; Maestú, Fernando; Ito, Kengo; Kato, Takashi

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ABSTRACT Biomarkers useful for the predementia stages of Alzheimer's disease are needed. Electroencephalography and magnetoencephalography (MEG) are expected to provide potential biomarker candidates for evaluating the predementia stages of Alzheimer's disease. However, the physiological relevance of EEG/MEG signal changes and their role in pathophysiological processes such as amyloid-β deposition and neurodegeneration need to be elucidated. We evaluated 28 individuals with mild cognitive impairment and 38 cognitively normal individuals, all of whom were further classified into amyloid-β-positive mild cognitive impairment (n = 17, mean age 74.7 ± 5.4 years, nine males), amyloid-β-negative mild cognitive impairment (n = 11, mean age 73.8 ± 8.8 years, eight males), amyloid-β-positive cognitively normal (n = 13, mean age 71.8 ± 4.4 years, seven males), and amyloid-β-negative cognitively normal (n = 25, mean age 72.5 ± 3.4 years, 11 males) individuals using Pittsburgh compound B-PET. We measured resting state MEG for 5 min with the eyes closed, and investigated regional spectral patterns of MEG signals using atlas-based region of interest analysis. Then, the relevance of the regional spectral patterns and their associations with pathophysiological backgrounds were analysed by integrating information from Pittsburgh compound B-PET, fluorodeoxyglucose-PET, structural MRI, and cognitive tests. The results demonstrated that regional spectral patterns of resting state activity could be separated into several types of MEG signatures as follows: (i) the effects of amyloid-β deposition were expressed as the alpha band power augmentation in medial frontal areas; (ii) the delta band power increase in the same region was associated with disease progression within the Alzheimer's disease continuum and was correlated with entorhinal atrophy and an Alzheimer's disease-like regional decrease in glucose metabolism; and (iii) the global theta power augmentation, which was previously considered to be an Alzheimer's disease-related EEG/MEG signature, was associated with general cognitive decline and hippocampal atrophy, but was not specific to Alzheimer's disease because these changes could be

observed in the absence of amyloid-β deposition. The results suggest that these MEG signatures may be useful as unique biomarkers for the predementia stages of Alzheimer's disease.

Brain: a journal of neurology (2018), Vol. 141, No. 5 (29522156)

Distinct spatiotemporal patterns of neuronal functional connectivity in primary progressive aphasia variants (2017)

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ABSTRACT Primary progressive aphasia is a syndrome characterized by progressive loss of language abilities with three main phenotypic clinical presentations, including logopenic, non-fluent/agrammatic, and semantic variants. Previous imaging studies have shown unique anatomic impacts within language networks in each variant. However, direct measures of spontaneous neuronal activity and functional integrity of these impacted neural networks in primary progressive aphasia are lacking. The aim of this study was to characterize the spatial and temporal patterns of resting state neuronal synchronizations in primary progressive aphasia syndromes. We hypothesized that resting state brain oscillations will show unique deficits within language network in each variant of primary progressive aphasia. We examined 39 patients with primary progressive aphasia including logopenic variant (n = 14, age = 61 ± 9 years), non-fluent/agrammatic variant (n = 12, age = 71 ± 8 years) and semantic variant (n = 13, age = 65 ± 7 years) using magnetoencephalographic imaging, compared to a control group that was matched in age and gender to each primary progressive aphasia subgroup (n = 20, age = 65 ± 5 years). Each patient underwent a complete clinical evaluation including a comprehensive battery of language tests. We examined the whole-brain resting state functional connectivity as measured by imaginary coherence in each patient group compared to the control cohort, in three frequency oscillation bands-delta-theta (2-8 Hz); alpha (8-12 Hz); beta (12-30 Hz). Each variant showed a distinct spatiotemporal pattern of altered functional connectivity compared to age-matched controls. Specifically, we found significant hyposynchrony of alpha and beta frequency within the left posterior temporal and occipital cortices in patients with the logopenic variant, within the left inferior frontal cortex in patients with the non-fluent/agrammatic variant, and within the left temporo-parietal junction in patients with the semantic variant. Patients with logopenic variant primary progressive aphasia also showed significant hypersynchrony of delta-theta frequency within bilateral medial frontal and posterior parietal cortices. Furthermore, region of interest-based analyses comparing the spatiotemporal patterns of variant-specific regions of interest identified in comparison to age-matched controls showed significant differences between primary progressive aphasia variants themselves. We also found distinct patterns of regional spectral power changes in each primary progressive aphasia variant, compared to age-matched controls. Our results demonstrate neurophysiological signatures of network-specific neuronal dysfunction in primary progressive aphasia variants. The unique spatiotemporal patterns of neuronal synchrony signify diverse neurophysiological disruptions and pathological underpinnings of the language network in each variant.

Keywords: dementia, magnetoencephalography, neural oscillations, primary progressive aphasia, resting state functional connectivity

Brain: a journal of neurology (2017), Vol. 140, No. 10 (28969381)

Loss of brain inter-frequency hubs in Alzheimer's disease (2019)

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ABSTRACT Alzheimer's disease (AD) causes alterations of brain network structure and function. The latter consists of connectivity changes between oscillatory processes at different frequency channels. We proposed a multi-layer network approach to analyze multiple-frequency brain networks inferred from magnetoencephalographic recordings during resting-states in AD subjects and age-matched controls. Main results showed that brain networks tend to facilitate information propagation across different frequencies, as measured by the multi-participation coefficient (MPC). However, regional connectivity in AD subjects was abnormally distributed across frequency bands as compared to controls, causing significant decreases of MPC. This effect was mainly localized in association areas and in the cingulate cortex, which acted, in the healthy group, as a true inter-frequency hub. MPC values significantly correlated with memory impairment of AD subjects, as measured by the total recall score. Most predictive regions belonged to components of the default-mode network that are typically affected by atrophy, metabolism disruption and amyloid-β deposition. We evaluated the diagnostic power of the MPC and we showed that it led to increased classification accuracy (78.39%) and sensitivity (91.11%). These findings shed new light on the brain functional alterations underlying AD and provide analytical tools for identifying multi-frequency neural mechanisms of brain diseases.

Scientific reports (2017), Vol. 7, No. 1 (28883408)

Early functional network alterations in asymptomatic elders at risk for Alzheimer's disease (2019)

Nakamura, Akinori; Cuesta, Pablo; Kato, Takashi; Arahata, Yutaka; Iwata, Kaori; Yamagishi, Misako; Kuratsubo, Izumi; Kato, Kimiko; Bundo, Masahiko; Diers, Kersten; Fernández, Alberto; Maestú, Fernando; Ito, Kengo

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ABSTRACT Amyloid-β (Aβ) deposition is known to starts decades before the onset of clinical symptoms of Alzheimer's disease (AD), however, the detailed pathophysiological processes underlying this preclinical period are not well understood. This study aimed to investigate functional network alterations in cognitively intact elderly individuals at risk for AD, and assessed the association between these network alterations and changes in Aβ deposition, glucose metabolism, and brain structure. Forty-five cognitively normal elderly subjects, who were classified into Aβ-positive (CN+) and Aβ-negative (CN-) groups using [11]C-Pittsburgh compound B PET, underwent resting state magnetoencephalography measurements, [18]F-fluorodeoxyglucose PET (FDG-PET) and structural MRI. Results demonstrated that in the CN+ group, functional connectivity (FC) within the precuneus was significantly decreased, whereas it was significantly enhanced between the precuneus and the bilateral inferior parietal lobules in the low-frequency bands (theta and delta). These changes were suggested to be associated with local cerebral Aβ deposition. Most of Aβ+ individuals in this study did not show any metabolic or anatomical changes, and there were no significant correlations between FC values and FDG-PET or MRI volumetry data. These results demonstrate that functional network alterations, which occur in association with Aβ deposition, are detectable

using magnetoencephalography before metabolic and anatomical changes are seen.

Scientific reports (2017), Vol. 7, No. 1 (28747760)

MEG biomarker of Alzheimer's disease: Absence of a prefrontal generator during auditory sensory gating (2018)

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ABSTRACT Magnetoencephalography (MEG), a direct measure of neuronal activity, is an underexplored tool in the search for biomarkers of Alzheimer's disease (AD). In this study, we used MEG source estimates of auditory gating generators, nonlinear correlations with neuropsychological results, and multivariate analyses to examine the sensitivity and specificity of gating topology modulation to detect AD. Our results demonstrated the use of MEG localization of a medial prefrontal (mPFC) gating generator as a discrete (binary) detector of AD at the individual level and resulted in recategorizing the participant categories in: (1) controls with mPFC generator localized in response to both the standard and deviant tones; (2) a possible preclinical stage of AD participants (a lower functioning group of controls) in which mPFC activation was localized to the deviant tone only; and (3) symptomatic AD in which mPFC activation was not localized to either the deviant or standard tones. This approach showed a large effect size (0.9) and high accuracy, sensitivity, and specificity (100%) in identifying symptomatic AD patients within a limited research sample. The present results demonstrate high potential of mPFC activation as a noninvasive biomarker of AD pathology during putative preclinical and clinical stages. Hum Brain Mapp 38:5180-5194, 2017. © 2017 Wiley Periodicals, Inc.

Keywords: Alzheimer's disease, Rey-Osterreith complex figure test, auditory sensory gating, biomarker, dementia, magnetoencephalography, mild cognitive impairment, neuroimaging, preclinical Alzheimer's disease, prefrontal cortex

Human brain mapping (2017), Vol. 38, No. 10 (28714589)

Directional information flow in patients with Alzheimer's disease. A source-space resting-state MEG study (2018)

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ABSTRACT In a recent magnetoencephalography (MEG) study, we found posterior-to-anterior information flow over the cortex in higher frequency bands in healthy subjects, with a reversed pattern in the theta band. A disruption of information flow may underlie clinical symptoms in Alzheimer's disease (AD). In AD, highly connected regions (hubs) in posterior areas are mostly disrupted. We therefore hypothesized that in AD the information flow from these hub regions would be disturbed. We used resting-state MEG recordings from 27 early-onset AD patients and 26 healthy controls. Using beamformer-based virtual electrodes, we estimated neuronal oscillatory activity for 78 cortical regions of interest (ROIs) and 12 subcortical ROIs of the AAL atlas, and calculated the directed phase transfer entropy (dPTE) as a measure of information flow between these ROIs. Group differences were evaluated using permutation tests and, for the AD group, associations between dPTE and general cognition or CSF biomarkers were determined using Spearman correlation coefficients. We confirmed the previously reported posterior-to-anterior information flow in the higher frequency bands in the healthy controls, and found it to be disturbed in

the beta band in AD. Most prominently, the information flow from the precuneus and the visual cortex, towards frontal and subcortical structures, was decreased in AD. These disruptions did not correlate with cognitive impairment or CSF biomarkers. We conclude that AD pathology may affect the flow of information between brain regions, particularly from posterior hub regions, and that changes in the information flow in the beta band indicate an aspect of the pathophysiological process in AD.

Keywords: Alzheimer's disease, Atlas-based beamforming, Information flow, Magnetoencephalography, Phase transfer entropy

NeuroImage. Clinical (2017), Vol. 15 (28702344)

Alzheimer's disease disrupts alpha and beta-band resting-state oscillatory network connectivity (2017)

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OBJECTIVE Neuroimaging studies in Alzheimer's disease (AD) yield conflicting results due to selective investigation. We conducted a comprehensive magnetoencephalography study of connectivity changes in AD and healthy ageing in the resting-state.

METHODS We performed a whole-brain, source-space assessment of oscillatory neural signalling in multiple frequencies comparing AD patients, elderly and young controls. We compared eyes-open and closed group oscillatory envelope activity in networks obtained through temporal independent component analysis, and calculated whole-brain node-based amplitude and phase connectivity.

RESULTS In bilateral parietotemporal areas, oscillatory envelope amplitude increased with healthy ageing, whereas both local amplitude and node-to-global connectivity decreased with AD. AD-related decreases were spatially specific and restricted to the alpha and beta bands. A significant proportion of the variance in areas of peak group difference was explained by cognitive integrity, in addition to group. None of the groups differed in phase connectivity. Results were highly similar for eyes-open and closed resting-state.

CONCLUSIONS These results support the disconnection syndrome hypothesis and suggest that AD shows distinct and unique patterns of disrupted neural functioning, rather than accelerated healthy ageing.

SIGNIFICANCE Whole-brain assessments show that disrupted regional oscillatory envelope amplitude and connectivity in the alpha and beta bands play a key role in AD.

Keywords: Alzheimer's disease, Default-mode network, Functional connectivity, Magnetoencephalography, Neural oscillations, Resting state

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MEG Beamformer-Based Reconstructions of Functional Networks in Mild Cognitive Impairment

López, Maria E; Engels, Marjolein M A; van Straaten, Elisabeth C W; Bajo, Ricardo; Delgado, María L; Scheltens, Philip; Hillebrand, Arjan; Stam, Cornelis J; Maestú, Fernando

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ABSTRACT Subjects with mild cognitive impairment (MCI) have an increased risk of developing Alzheimer's disease (AD), and their functional brain networks are presumably already altered. To test this hypothesis, we compared magnetoencephalography (MEG) eyes-closed resting-state recordings from 29 MCI subjects and 29 healthy elderly subjects in the present exploratory study. Functional connectivity in different frequency bands was assessed with the phase lag index (PLI) in source space. Normalized weighted clustering coefficient (normalized Cw) and path length (normalized Lw), as well as network measures derived from the minimum spanning tree [MST; i.e., betweenness centrality (BC) and node degree], were calculated. First, we found altered PLI values in the lower and upper alpha bands in MCI patients compared to controls. Thereafter, we explored network differences in these frequency bands. Normalized Cw and Lw did not differ between the groups, whereas BC and node degree of the MST differed, although these differences did not survive correction for multiple testing using the False Discovery Rate (FDR). As an exploratory study, we may conclude that: (1) the increases and decreases observed in PLI values in lower and upper alpha bands in MCI patients may be interpreted as a dual pattern of disconnection and aberrant functioning; (2) network measures are in line with connectivity findings, indicating a lower efficiency of the brain networks in MCI patients; (3) the MST centrality measures are more sensitive to detect subtle differences in the functional brain networks in MCI than traditional graph theoretical metrics.

Keywords: brain networks, magnetoencephalography, mild cognitive impairment, minimum spanning tree, phase lag index

Frontiers in aging neuroscience (2017), Vol. 9 (28487647)

Functional Connectivity Disruption in Subjective Cognitive Decline and Mild Cognitive Impairment: A Common Pattern of Alterations

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ABSTRACT Functional connectivity (FC) alterations represent a key feature in Alzheimer's Disease (AD) and provide a useful tool to characterize and predict the course of the disease. Those alterations have been also described in Mild Cognitive Impairment (MCI), a prodromal stage of AD. There is a growing interest in detecting AD pathology in the brain in the very early stages of the disorder. Subjective Cognitive Decline (SCD) could represent a preclinical asymptomatic stage of AD but very little is known about this population. In the present work we assessed whether FC disruptions are already present in this stage, and if they share any spatial distribution properties with MCI alterations (a condition known to be highly related to AD). To this end, we measured electromagnetic spontaneous activity with MEG in 39 healthy control elders, 41 elders with SCD and 51 MCI patients. The results showed FC alterations in both SCD and MCI compared to the healthy control group. Interestingly, both groups exhibited a very similar spatial pattern of altered links: a hypersynchronized anterior network and a posterior network characterized by a decrease in FC. This decrease was

more pronounced in the MCI group. These results highlight that elders with SCD present FC alterations. More importantly, those disruptions affected AD typically related areas and showed great overlap with the alterations exhibited by MCI patients. These results support the consideration of SCD as a preclinical stage of AD and may indicate that FC alterations appear very early in the course of the disease.

Keywords: Alzheimer disease, Functional connectivity, Subjective Cognitive Decline, magnetoencephalography, mild cognitive impairment

Frontiers in aging neuroscience (2017), Vol. 9 (28484387)

Selective impairment of hippocampus and posterior hub areas in Alzheimer's disease: an MEG-based multiplex network study (2017)

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ABSTRACT Although frequency-specific network analyses have shown that functional brain networks are altered in patients with Alzheimer's disease, the relationships between these frequency-specific network alterations remain largely unknown. Multiplex network analysis is a novel network approach to study complex systems consisting of subsystems with different types of connectivity patterns. In this study, we used magnetoencephalography to integrate five frequency-band specific brain networks in a multiplex framework. Previous structural and functional brain network studies have consistently shown that hub brain areas are selectively disrupted in Alzheimer's disease. Accordingly, we hypothesized that hub regions in the multiplex brain networks are selectively targeted in patients with Alzheimer's disease in comparison to healthy control subjects. Eyes-closed resting-state magnetoencephalography recordings from 27 patients with Alzheimer's disease (60.6 ± 5.4 years, 12 females) and 26 controls (61.8 ± 5.5 years, 14 females) were projected onto atlas-based regions of interest using beamforming. Subsequently, source-space time series for both 78 cortical and 12 subcortical regions were reconstructed in five frequency bands (delta, theta, alpha 1, alpha 2 and beta band). Multiplex brain networks were constructed by integrating frequency-specific magnetoencephalography networks. Functional connections between all pairs of regions of interests were quantified using a phase-based coupling metric, the phase lag index. Several multiplex hub and heterogeneity metrics were computed to capture both overall importance of each brain area and heterogeneity of the connectivity patterns across frequency-specific layers. Different nodal centrality metrics showed consistently that several hub regions, particularly left hippocampus, posterior parts of the default mode network and occipital regions, were vulnerable in patients with Alzheimer's disease compared to control subjects. Of note, these detected vulnerable hubs in Alzheimer's disease were absent in each individual frequency-specific network, thus showing the value of integrating the networks. The connectivity patterns of these vulnerable hub regions in the patients were heterogeneously distributed across layers. Perturbed cognitive function and abnormal cerebrospinal fluid amyloid-β42 levels correlated positively with the vulnerability of the hub regions in patients with Alzheimer's disease. Our analysis therefore demonstrates that the magnetoencephalography-based multiplex brain networks contain important information that cannot be revealed by frequency-specific brain networks. Furthermore, this indicates that functional networks obtained in different frequency bands do not act as independent entities. Overall, our multiplex network study provides an effective framework to integrate the frequency-specific networks with different frequency patterns and reveal neuropathological mechanism of hub disruption in Alzheimer's disease.

Keywords: Alzheimer's disease, heterogeneity, hubs, magnetoencephalography, multiplex network

Brain: a journal of neurology (2017), Vol. 140, No. 5 (28334883)

Depression

Spectral fingerprints of facial affect processing bias in major depression disorder (2020)

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ABSTRACT In major depressive disorder (MDD), processing of facial affect is thought to reflect a perceptual bias (toward negative emotion, away from positive emotion, and interpretation of neutral as emotional). However, it is unclear to what extent and which specific perceptual bias is represented in MDD at the behavior and neuronal level. The present report examined 48 medication naive MDD patients and 41 healthy controls (HCs) performing a facial affect judgment task while magnetoencephalography was recorded. MDD patients were characterized by overall slower response times and lower perceptual judgment accuracies. In comparison with HC, MDD patients exhibited less somatosensory beta activity (20-30 Hz) suppression, more visual gamma activity (40-80 Hz) modulation and somatosensory beta and visual gamma interaction deficit. Moreover, frontal gamma activity during positive facial expression judgment was found to be negatively correlated with depression severity. Present findings suggest that perceptual bias in MDD is associated with distinct spatio-spectral manifestations on the neural level, which potentially establishes aberrant pathways during facial emotion processing and contributes to MDD pathology.

Keywords: beta activity, gamma activity, magnetoencephalography (MEG), major depressive disorder (MDD), perceptual bias

Social cognitive and affective neuroscience (2019), Vol. 14, No. 11 (31850496)

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)

Hyperactive frontolimbic and frontocentral resting-state gamma connectivity in major depressive disorder (2020)

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BACKGROUND Major depressive disorder (MDD) is a system-level disorder affecting multiple functionally integrated cerebral networks. Nevertheless, their temporospatial organization and potential disturbance remain mostly unknown. The present report tested the hypothesis that deficient temporospatial network organization separates MDD and healthy controls (HC), and is linked to symptom severity of the disorder.

METHODS Eyes-closed resting-state magnetoencephalographic (MEG) recordings were obtained from twenty-two MDD and twenty-two HC subjects. Beamforming source localization and functional connectivity analysis were applied to identify frequency-specific network interactions. Then, a novel virtual cortical resection approach was used to pinpoint putatively critical network controllers, accounting for aberrant cerebral connectivity patterns in MDD.

RESULTS We found significantly elevated frontolimbic and frontocentral connectivity mediated by gamma (30-48 Hz) activity in MDD versus HC, and the right amygdala was the key differential network controller accounting for aberrant cerebral connectivity patterns in MDD. Furthermore, this frontolimbic and frontocentral gamma-band hyper-connectivity was positively correlated with depression severity.

LIMITATIONS The overall sample size was small, and we found significant effects in the deep limbic regions with resting-state MEG, the reliability of which was difficult to corroborate further.

CONCLUSIONS Overall, these findings support a notion that the right amygdala critically controls the exaggerated gamma-band frontolimbic and frontocentral connectivity in MDD during the resting-state condition, which potentially constitutes pre-established aberrant pathways during task processing and contributes to MDD pathology.

Journal of affective disorders (2019), Vol. 257 (31299407)

Multimodal imaging reveals a complex pattern of dysfunction in corticolimbic pathways in major depressive disorder (2020)

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ABSTRACT Major depressive disorder (MDD) is highly prevalent and associated with considerable morbidity, yet its pathophysiology remains only partially understood. While numerous studies have investigated the neurobiological correlates of MDD, most have used only a single neuroimaging modality. In particular, diffusion tensor imaging (DTI) studies have failed to yield uniform results. In this context, examining key tracts and using information from multiple neuroimaging modalities may better characterize potential abnormalities in the MDD brain. This study analyzed data from 30 participants with MDD and 26 healthy participants who underwent DTI, magnetic resonance spectroscopy (MRS), resting-state functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG). Tracts connecting the subgenual anterior cingulate cortex (sgACC) and the left and right amygdala, as well as connections to the left and right hippocampus and thalamus, were examined as target areas. Reduced fractional anisotropy (FA) was observed in the studied tracts. Significant differences in the correlation between medial prefrontal glutamate concentrations and FA were also observed between MDD and healthy participants along tracts connecting the sgACC and right amygdala; healthy participants exhibited a strong correlation but MDD participants showed no such relationship. In the same tract, a correlation was observed between FA and subsequent antidepressant response to ketamine infusion in MDD participants. Exploratory models also suggested group differences in the relationship between DTI, fMRI, and MEG measures. This study is the first to combine MRS, DTI, fMRI, and MEG data to obtain multimodal indices of MDD and antidepressant response and may lay the foundation for similar future analyses.

Keywords: diffusion tensor imaging, functional magnetic resonance imaging, magnetic resonance spectroscopy, magnetoencephalography, major depressive disorder, multimodal

Human brain mapping (2019), Vol. 40, No. 13 (31179620)

Identification of major depressive disorder and prediction of treatment response using functional connectivity between the prefrontal cortices and subgenual anterior cingulate: A real-world study (2020)

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BACKGROUND Major depressive disorder (MDD) is associated with a heavy disease burden due to the difficulty in diagnosing the disorder and the uncertainty of treatment outcomes. Previous studies have demonstrated the value of functional connectivity (FC) between the dorsolateral prefrontal cortex (DLPFC) and the subgenual anterior cingulate cortex (sgACC) in the identification of MDD and the prediction of antidepressant efficacy. In the present study, we aimed to investigate whether FC is helpful in discriminating patients from healthy controls and in predicting treatment outcome.

METHODS Seventy-six medication-free patients with MDD and 28 healthy controls were enrolled in the study. Magnetoencephalography (MEG) and the Hamilton Rating Score for Depression (HRSD-17) were administered at baseline. Then, the HRSD-17 was assessed weekly until each patient met the remission criteria, defined as a total HRSD-17 score ≤ 7. Time-dependent

Cox regression analysis was used to evaluate the association between FC and the incidence of remission.

RESULTS Healthy controls and MDD patients had opposite FC patterns; this may be helpful for identifying MDD (AUC = 0.8, p < 0.001, sensitivity 85.7%, specificity 67.9%). Alpha connectivity between the DLPFC and sgACC (HR 1.858, 95%CI 1.013-3.408, p = 0.045) was found to be an independent factor associated with better final antidepressant outcome.

LIMITATIONS This study was conducted in a small sample of subjects. Further, the direction of regulation between the DLPFC and sgACC was not considered.

CONCLUSIONS FC may help identify depression and may be related to the severity of depressive symptoms and predict the efficacy of antidepressant treatment.

Keywords: Alpha, Antidepressants, Connectivity, MDD, MEG, Remission

Journal of affective disorders (2019), Vol. 252 (30999093)

Dynamic community structure in major depressive disorder: A resting-state MEG study (2019)

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BACKGROUND Major Depressive Disorder (MDD), characterized by depressed mood or anhedonia, is associated with altered functional connectivity (FC) within and between large scale networks such as the Default Mode Network (DMN), the Central Executive Network (CEN) and the Salience Network (SN). Since aberrant FC exhibits temporal variability and could give rise to distorted reconfiguration of functional brain networks, an in-depth analysis of the community structure could provide further insight into the synchrony of networks. We hypothesized that alterations in dynamic network community structure in MDD could be temporally accompanied by disrupted conscious states of these three networks.

METHODS 26 MDD patients and 25 healthy controls were scanned using a whole-head resting-state Magnetoencephalography (MEG) machine. A novel multilayer modularity framework explored the functional modulation of these networks. Recruitment (R) and integration (I) provided the strength of interaction within networks or across networks, respectively.

RESULTS The brain regions in the DMN, CEN and SN were transiently integrated and segmented in both patients and controls. R of CEN and I of SN were significantly greater in MDD compared to controls.

CONCLUSION Intrinsic resting-state networks dynamically interact and reorganize into distinct functional modules in both patients and controls. However, the CEN "hyper-intertwines" with itself and SN "hyper-integrates" among the network of interest in depressed patients compared to controls. Network-level alterations in R and I revealed a more generalized system-level effect rather than a focal-wise effect from a neural dynamic perspective. This could potentially highlight an abnormal network-based mechanism in depression.

Keywords: Community structure, Default Mode Network (DMN);Central Executive Network (CEN), Major Depressive Disorder (MDD), Salience Network (SN)

Progress in neuro-psychopharmacology & biological psychiatry (2019), Vol. 92 (30572002)

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)

Synaptic potentiation and rapid antidepressant response to ketamine in treatment-resistant major depression: A replication study (2019)

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ABSTRACT Preclinical and clinical evidence has demonstrated that ketamine has rapid antidepressant effects. Studies using pre-treatment with an AMPA inhibitor suggest that enhancing AMPA throughput is crucial to ketamine's effects, including increases in both basal and evoked gamma power. This study sought to replicate previous findings of increased gamma response to a somatosensory stimulus at 230 min and Day 1 in ketamine responders versus non-responders in 31 depressed subjects and 25 healthy controls. A significant difference in peak gamma power was seen in the depressed ketamine responders versus non-responders. These results implicate AMPA throughput in ketamine's mechanism of antidepressant action.

Keywords: Depression, Ketamine, Magnetoencephalography (MEG)

Psychiatry research. Neuroimaging (2019), Vol. 283 (30551012)

Neurophysiological Changes Associated with Antidepressant Response to Ketamine Not Observed in a Negative Trial of Scopolamine in Major Depressive Disorder (2019)

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BACKGROUND This randomized, placebo-controlled, crossover trial examined the antidepressant efficacy of the muscarinic antagonist scopolamine in major depressive disorder subjects with more severe and refractory forms of major depressive disorder relative to previous reports.

METHODS Participants included 23 medication-free major depressive disorder subjects (12 F/11 M, 20-55 years) currently experiencing a major depressive episode. Subjects had scored ≥20 on the Montgomery-Asberg Depression Rating Scale. Following a single-blind, placebo lead-in, participants were randomized to receive 2 counterbalanced blocks of 3 i.v. infusions of scopolamine (4 μg/kg) and placebo in a double-blind manner. The primary and secondary outcomes were the Montgomery-Asberg Depression Rating Scale and the Hamilton Anxiety Rating Scale, respectively. Magnetoencephalography and plasma brain-derived neurotrophic factor concentrations were obtained prior to and after each treatment phase.

RESULTS As assessed by both the Montgomery-Asberg Depression Rating Scale and Hamilton Anxiety Rating Scale, scopolamine had no significant antidepressant or anxiolytic effects relative to placebo. No significant drug vs placebo effects were seen in magnetoencephalography gamma power or brain-derived neurotrophic factor plasma concentrations, and brain-derived neurotrophic factor changes did not correlate with change in Montgomery-Asberg Depression Rating Scale score in response to scopolamine.

CONCLUSIONS These results do not support the efficacy of scopolamine for more severe or refractory forms of depression. No pre- to post-infusion changes in plasma brain-derived neurotrophic factor were detected, and magnetoencephalography gamma power changed only in the placebo lead-in, suggesting that these biomarker measures were not affected by scopolamine in this cohort. While difficult to interpret given the lack of antidepressant response, the findings suggest that the neurobiological effects of ketamine and scopolamine are at least partly distinct.

The international journal of neuropsychopharmacology (2019), Vol. 22, No. 1 (30184133)

Complexity analysis of spontaneous brain activity in mood disorders: A magnetoencephalography study of bipolar disorder and major depression (2019)

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BACKGROUND AND PURPOSE The lack of a biomarker for Bipolar Disorder (BD) causes problems in the differential diagnosis with other mood disorders such as major depression (MD), and misdiagnosis frequently occurs. Bearing this in mind, we investigated non-linear magnetoencephalography (MEG) patterns in BD and MD.

METHODS Lempel-Ziv Complexity (LZC) was used to evaluate the resting-state MEG activity in a cross-sectional sample of 60 subjects, including 20 patients with MD, 16 patients with BD type-I, and 24 control (CON) subjects. Particular attention was paid to the role of age. The results were aggregated by scalp region.

RESULTS Overall, MD patients showed significantly higher LZC scores than BD patients and CONs. Linear regression analyses demonstrated distinct tendencies of complexity progression as a function of age, with BD patients showing a divergent tendency as compared with MD and CON groups. Logistic regressions confirmed such distinct relationship with age, which allowed the classification of diagnostic groups.

CONCLUSIONS The patterns of neural complexity in BD and MD showed not only quantitative differences in their non-linear MEG characteristics but also divergent trajectories of progression as a function of age. Moreover, neural complexity patterns in BD patients resembled those previously observed in schizophrenia, thus supporting preceding evidence of common neuropathological processes.

Keywords: Bipolar disorder, Lempel-Ziv Complexity, Magnetoencephalography, Mood disorders, Psychosis Continuum

Comprehensive psychiatry (2018), Vol. 84 (29734005)

Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects (2020)

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ABSTRACT Ketamine's mechanism of action was assessed using gamma power from magnetoencephalography (MEG) as a proxy measure for homeostatic balance in 35 unmedicated subjects with major depressive disorder (MDD) and 25 healthy controls enrolled in a double-blind, placebo-controlled, randomized crossover trial of 0.5 mg/kg ketamine. MDD subjects showed significant improvements in depressive symptoms, and healthy control subjects exhibited modest but significant increases in depressive symptoms for up to 1 day after ketamine administration. Both groups showed increased resting gamma power following ketamine. In MDD subjects, gamma power was not associated with the magnitude of the antidepressant effect. However, baseline gamma power was found to moderate the relationship between post-ketamine gamma power and antidepressant response; specifically, higher post-ketamine gamma power was associated with better response in MDD subjects with lower baseline gamma, with an inverted relationship in MDD subjects with higher baseline gamma. This relationship was observed in multiple regions involved in networks hypothesized to be involved in the pathophysiology of MDD. This finding suggests biological subtypes based on the direction of homeostatic dysregulation and has important implications for inferring ketamine's mechanism of action from studies of healthy controls alone.

Molecular psychiatry (2019), Vol. 24, No. 7 (29487402)

A supplementary functional connectivity microstate attached to the default mode network in depression revealed by resting-state magnetoencephalography (2019)

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ABSTRACT Default mode network (DMN) has discernable involvement in the representation of negative, self-referential information in depression. Both increased and decreased resting-state functional connectivity between the anterior and posterior DMN have been observed in depression. These conflicting connectivity differences necessitated further exploration of the resting-state DMN dysfunction in depression. Hence, we investigated the time-varying dynamic interactions within the DMN via functional connectivity microstates in a sub-second level. 25 patients with depression and 25 matched healthy controls were enrolled in the MEG analysis. Spherical K-means algorithms embedded within an iterative optimization frame were applied to sliding windowed correlation matrices, resulting in sub-second alternations of two functional connectivity microstates for groups and highlighting the presence of functional variability. In the power dominant state, depressed patients showed a transient decreased pattern that reflected inter/intra-subnetwork deregulation. A supplementary negatively correlated state simultaneously presented with increased connectivity between the ventromedial prefrontal cortex (vmPFC) and the posterior cingulate cortex (PCC), two core nodes for the anterior and posterior DMN respectively. Additionally, depressed patients stayed longer in the supplementary microstate compared to healthy controls. During the time spent in the supplementary microstate, an attempt to compensate for the aberrant effect of vmPFC on PCC across DMN subnetworks was possibly made to balance the self-related processes disturbed by the dominant pattern. The functional compensation mechanism of the supplementary microstate attached to the dominant disrupted one provided a possible explanation to the existing inconsistent findings between the anterior and posterior DMN in depression.

Keywords: Default mode network, Depression, Dynamic, Magnetoencephalography, Microstates, Resting-state functional connectivity

Progress in neuro-psychopharmacology & biological psychiatry (2018), Vol. 83 (29330134)

Risk of depression enhances auditory Pitch discrimination in the brain as indexed by the mismatch negativity (2017)

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OBJECTIVE Depression is a state of aversion to activity and low mood that affects behaviour, thoughts, feelings and sense of well-being. Moreover, the individual depression trait is associated with altered auditory cortex activation and appraisal of the affective content of sounds.

METHODS Mismatch negativity responses (MMNs) to acoustic feature changes (pitch, timbre, location, intensity, slide and rhythm) inserted in a musical sequence played in major or minor mode were recorded using magnetoencephalography (MEG) in 88 subclinical participants with depression risk.

RESULTS We found correlations between MMNs to slide and pitch and the level of depression risk reported by participants, indicating that higher MMNs correspond to higher risk of depression. Furthermore we found significantly higher MMN amplitudes to mistuned pitches within a major context compared to MMNs to pitch changes in a minor context.

CONCLUSIONS The brains of individuals with depression risk are more responsive to mistuned and fast pitch stimulus changes, even at a pre-attentive level.

SIGNIFICANCE Considering the altered appraisal of affective contents of sounds in depression and the relevance of spectral pitch features for those contents in music and speech, we propose that individuals with subclinical depression risk are more tuned to tracking sudden pitch changes.

Keywords: Depression, Magnetoenchephalography (MEG), Mismatch negativity, Musical multi-feature paradigm, Pitch

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2017), Vol. 128, No. 10 (28826023)

Right hemisphere pitch-mismatch negativity reduction in patients with major depression: An MEG study (2017)

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BACKGROUND The mismatch negativity (MMN) component of the event-related potential and its magnetic counterpart, the MMNm, are generated by a mismatch between the physical features of a deviant stimulus and a neuronal sensory-memory trace produced by repetitive standard stimuli. Deficits in the MMN/MMNm have been reported in patients with major depression; however, the results are inconsistent. The present study investigated the pitch-MMNm in patients with major depression using whole-head 306-channel magnetoencephalography (MEG).

METHODS Twenty patients with major depression and 36 healthy subjects participated in this study. Subjects were presented with two sequences of auditory stimuli. One consisted of 1000Hz standard signals (probability=90%) and 1200Hz deviant signals (probability=10%), while the other consisted of 1200Hz standard (90%) and 1000Hz deviant signals (10%). Event-related brain responses to standard tones were subtracted from responses to deviant tones.

RESULTS Major depressive patients showed significantly reduced magnetic global field power (GFP) of MMNm in the right hemisphere ($p=0.02$), although no significant MMNm reduction was observed in the left hemisphere ($p=0.81$). Additionally, patients with major depression showed significantly earlier bilateral MMNm peak latencies ($p=0.004$). No significant associations were observed between MMNm variables and demographic data/clinical variables within the patients.

LIMITATIONS We could not exclude the effects of antidepressants, mood stabilizers, or neuroleptics on the MMNm abnormalities found in patients with major depression. Sample size was also insufficient to permit subgroup analyses.

CONCLUSIONS Patients with major depression exhibited reduced GFP of MMNm in the right hemisphere. The present study suggested that patients with major depression may have right hemispheric dominant preattentive dysfunction.

Keywords: Magnetoencephalography, Major depression, Mismatch negativity, Preattentive dysfunction

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Maternal Depression Across the First Years of Life Impacts the Neural Basis of Empathy in Preadolescence (2017)

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OBJECTIVE Exposure to maternal depression across the first years of life markedly increases children's susceptibility to psychopathology, yet no study has tested its effects on the maturation of children's social brain.

METHOD Using a birth cohort of mothers with no contextual risk (N = 1,983), families were followed at 7 time points from birth to 11 years and repeatedly assessed for maternal depression across the first 6 years to form 2 cohorts: mothers continuously depressed from birth to 6 years and controls without depression. At 11 years of age, children's (n = 72; depressed, n = 27; nondepressed, n = 45) brain response to others' pain was measured by magnetoencephalography.

RESULTS Preadolescents displayed a unique oscillatory pattern with higher alpha power to pain versus no pain expressing as alpha rebound, not alpha suppression, at a late time window (1,100-1,300 ms post-stimulus) in the supplementary motor area. This suggests that top-down processing in areas of the pain matrix can underpin the maturation of vicarious empathy. Children of mothers with depression showed enhanced alpha rebound to pain in the right posterior superior temporal gyrus, which was unrelated to emotion detection abilities, pointing to decreased late processing of others' overwhelming experiences in socio-cognitive areas. Alpha power in the posterior superior temporal gyrus was predicted by higher maternal intrusiveness and lower synchrony across early childhood.

CONCLUSION These findings, from the first study to examine maternal depression and early caregiving as long-term predictors of children's neural empathic response, pinpoint a decrease in top-down socio-cognitive mechanisms as potential pathways for the cross-generational transfer of vulnerability from mothers with depression to their offspring and highlight the need for early interventions focused on enhancing maternal attunement.

Keywords: alpha oscillations, empathy, magnetoencephalography, maternal depression, mother–child interaction

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Dyslexia

Increased variability of stimulus-driven cortical responses is associated with genetic variability in children with and without dyslexia (2019)

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ABSTRACT Individuals with dyslexia exhibit increased brainstem variability in response to sound. It is unknown as to whether increased variability extends to neocortical regions associated with audition and reading, extends to visual stimuli, and whether increased variability characterizes all children with dyslexia or, instead, a specific subset of children. We evaluated the consistency of stimulus-evoked neural responses in children with (N = 20) or without dyslexia (N = 12) as measured by magnetoencephalography (MEG). Approximately half of the children with dyslexia had significantly higher levels of variability in cortical responses to both auditory and visual stimuli in multiple nodes of the reading network. There was a significant and positive relationship between the number of risk alleles at rs6935076 in the dyslexia-susceptibility gene KIAA0319 and the degree of neural variability in primary auditory cortex across all participants. This gene has been linked with neural variability in rodents and in typical readers. These findings indicate that unstable representations of auditory and visual stimuli in auditory and other reading-related neocortical regions are present in a subset of children with dyslexia and support the link between the gene KIAA0319 and the auditory neural variability across children with or without dyslexia.

Keywords: KIAA0319, gene, mechanisms, neural variability, reading, subgroups

Developmental cognitive neuroscience (2018), Vol. 34 (29894888)

Aberrant resting-state functional brain networks in dyslexia: Symbolic mutual information analysis of neuromagnetic signals (2019)

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ABSTRACT Neuroimaging studies have identified a variety of structural and functional connectivity abnormalities in students experiencing reading difficulties. The present study adopted a novel approach to assess the dynamics of resting-state neuromagnetic recordings in the form of symbolic sequences (i.e., repeated patterns of neuromagnetic fluctuations within and/or between sensors). Participants were 25 students experiencing severe reading difficulties (RD) and 27 age-matched non-impaired readers (NI) aged 7-14 years. Sensor-level data were first represented as symbolic sequences in eight conventional frequency bands. Next, dominant types of sensor-to-sensor interactions in the form of intra and cross-frequency coupling were

computed and subjected to graph modeling to assess group differences in global network characteristics. As a group RD students displayed predominantly within-frequency interactions between neighboring sensors which may reflect reduced overall global network efficiency and cost-efficiency of information transfer. In contrast, sensor networks among NI students featured a higher proportion of cross-frequency interactions. Brain-reading achievement associations highlighted the role of left hemisphere temporo-parietal functional networks, at rest, for reading acquisition and ability.

Keywords: Connectomics, Dyslexia, Functional connectivity, Graph theory, Intrinsic coupling modes, Magnetoencephalography (MEG), Symbolic dynamics

International journal of psychophysiology: official journal of the International Organization of Psychophysiology (2018), Vol. 126 (29476872)

Data-Driven Topological Filtering Based on Orthogonal Minimal Spanning Trees: Application to Multigroup Magnetoencephalography Resting-State Connectivity (2018)

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ABSTRACT In the present study, a novel data-driven topological filtering technique is introduced to derive the backbone of functional brain networks relying on orthogonal minimal spanning trees (OMSTs). The method aims to identify the essential functional connections to ensure optimal information flow via the objective criterion of global efficiency minus the cost of surviving connections. The OMST technique was applied to multichannel, resting-state neuromagnetic recordings from four groups of participants: healthy adults (n = 50), adults who have suffered mild traumatic brain injury (n = 30), typically developing children (n = 27), and reading-disabled children (n = 25). Weighted interactions between network nodes (sensors) were computed using an integrated approach of dominant intrinsic coupling modes based on two alternative metrics (symbolic mutual information and phase lag index), resulting in excellent discrimination of individual cases according to their group membership. Classification results using OMST-derived functional networks were clearly superior to results using either relative power spectrum features or functional networks derived through the conventional minimal spanning tree algorithm.

Keywords: brain networks, network topology, optimization of information flow, resting state, topological filtering

Brain connectivity (2017), Vol. 7, No. 10 (28891322)

Epilepsy

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

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Changes of Ictal-Onset Epileptic Network Synchronicity in Childhood Absence Epilepsy: A Magnetoencephalography Study

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ABSTRACT Objective: To further understand the mechanisms underlying epileptic network and the characteristics of individual specific network, we conducted a study on brain network by magnetoencephalography (MEG) focusing on patients with childhood absence

epilepsy (CAE). Methods: The network connectivity of 22 patients was investigated with MEG at the source level. Network connectivity of spikes and slow waves was computed with accumulated source imaging (ASI) and correlation analysis. Time-frequency analysis was used to characterize the network changes during the ictal-onset period of each patient and the potential factors. Results: We found that spectral power increased at around 1 s and distributed at 2-4 Hz in all patients. Ictal spikes simultaneously showed elevation of network connectivity, predominantly excitatory connections, when generalized firing activity spread to the overall brain. High-frequency oscillations (HFOs) were prone to detect overexcited neuronal firing in certain focal areas. Conclusions: Personal network changes during ictal onset had unique features in the time range and parallel seizure rhythm uniformly in every patient. There was an important time point for generalized discharges of the epileptic network. Ictal spiking activity played an important role in the epileptic network synchronicity of childhood absence epilepsy. Frequency oscillations provided references for locating abnormal changes in neuromagnetic signals.

Keywords: childhood absence epilepsy, epileptic network, ictal spikes, individual specific network, synchronicity

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Removal of Interictal MEG-Derived Network Hubs Is Associated With Postoperative Seizure Freedom

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ABSTRACT Objective: To investigate whether MEG network connectivity was associated with epilepsy duration, to identify functional brain network hubs in patients with refractory focal epilepsy, and assess if their surgical removal was associated with post-operative seizure freedom. Methods: We studied 31 patients with drug refractory focal epilepsy who underwent resting state magnetoencephalography (MEG), and structural magnetic resonance imaging (MRI) as part of pre-surgical evaluation. Using the structural MRI, we generated 114 cortical regions of interest, performed surface reconstruction and MEG source localization. Representative source localized signals for each region were correlated with each other to generate a functional brain network. We repeated this procedure across three randomly chosen one-minute epochs. Network hubs were defined as those with the highest intra-hemispheric mean correlations. Post-operative MRI identified regions that were surgically removed. Results: Greater mean MEG network connectivity was associated with a longer duration of epilepsy. Patients who were seizure free after surgery had more hubs surgically removed than patients who were not seizure free (AUC = 0.76, p = 0.01) consistently across three randomly chosen time segments. Conclusion: Our results support a growing literature implicating network hub involvement in focal epilepsy, the removal of which by surgery is associated with greater chance of post-operative seizure freedom.

Keywords: MEG (magnetoencephalography), epilepsy, network, outcome prediction, surgery

Frontiers in neurology (2020), Vol. 11 (33071948)

The relationship between neuromagnetic activity and cognitive function in benign childhood epilepsy with centrotemporal spikes (2021)

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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)

Towards the Automatic Localization of the Irritative Zone Through Magnetic Source Imaging (2021)

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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

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Frequency-Dependent Interictal Neuromagnetic Activities in Children With Benign Epilepsy With Centrotemporal Spikes: A Magnetoencephalography (MEG) Study

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ABSTRACT Objective: This study aimed to investigate interictal neuromagnetic activities in the low- to high-frequency ranges in patients with benign epilepsy with centrotemporal spikes (BECTS), especially those without interictal epileptiform discharges (IEDs). Methods: We studied 21 clinically-diagnosed BECTS patients and 11 age-matched healthy controls (HC) using high-sampling magnetoencephalography (MEG). Neuromagnetic sources were assessed with accumulated source imaging (ASI). The MEG data were analyzed in seven frequency bands. The MEG recordings distinguished BECTS without IEDs (n = 10) from those with IEDs (n = 11) and HC (n = 11). Results: At 1-4 Hz, the neuromagnetic activities in healthy subjects tended to locate at the precuneus/posterior cingulate, while those of the BECTS patients without IEDs tended to locate at the medial frontal cortex (MFC) compared to BECTS patients with IEDs. The MEG source imaging at 30-80 Hz revealed that BECTS patients without IEDs had higher occurrences of interictal brain activity in the medial temporal lobe (MTL) compared to controls and the brain activity strength seemed to be weaker. There was a significant correlation between the source strength of the interictal gamma oscillations of BECTS patients without IEDs and the duration of epilepsy. Conclusions: IEDs might disrupt the default mode network (DMN). Aberrant brain activities in BECTS patients without IEDs were associated with cognitive areas of the brain. The strength of gamma oscillations in the chronic epilepsy state reflected the duration of BECTS. Significance: MEG could reveal the aberrant neural activities in BECTS patients during the interictal period, and such abnormality is frequency-dependent. Gamma oscillations could be used to identify BECTS patients without IEDs.

Keywords: benign epilepsy with centrotemporal spikes, interictal epileptiform discharges, low- to high-frequency bands, magnetic source imaging, magnetoencephalography

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Sensitivity of magnetoencephalography as a diagnostic tool for epilepsy: a prospective study (2021)

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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)

Identifying the epileptogenic zone by four non-invasive imaging techniques versus stereo-EEG in MRI-negative pre-surgery epilepsy patients (2021)

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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

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Energy landscape of resting magnetoencephalography reveals fronto-parietal network impairments in epilepsy

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ABSTRACT Juvenile myoclonic epilepsy (JME) is a form of idiopathic generalized epilepsy. It is yet unclear to what extent JME leads to abnormal network activation patterns. Here, we characterized statistical regularities in magnetoencephalograph (MEG) resting-state networks and their differences between JME patients and controls by combining a pairwise maximum entropy model (pMEM) and novel energy landscape analyses for MEG. First, we fitted the pMEM to the MEG oscillatory power in the front-oparietal network (FPN) and other resting-state networks, which provided a good estimation of the occurrence probability of network states. Then, we used energy values derived from the pMEM to depict an energy landscape, with a higher energy state corresponding to a lower occurrence probability. JME patients showed fewer local energy minima than controls and had elevated energy values for the FPN within the theta, beta, and gamma bands. Furthermore, simulations of the fitted pMEM showed that the proportion of time the FPN was occupied within the basins of energy minima was shortened in JME patients. These network alterations were highlighted by significant classification of individual participants employing energy values as multivariate features. Our findings suggested that JME patients had altered multistability in selective functional networks and frequency bands in the fronto-parietal cortices.

Keywords: Energy landscape, Juvenile myoclonic epilepsy, MEG, Maximum entropy model, Resting-state networks

Network neuroscience (Cambridge, Mass.) (2020), Vol. 4, No. 2 (32537532)

Evidence From Meta-Analysis Supports Ictal Magnetoencephalographic Source Imaging as an Accurate Method in Presurgery Evaluation of Patients With Drug-Resistant Epilepsy (2021)

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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 desirable. 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)

Lateralization of epilepsy using intra-hemispheric brain networks based on resting-state MEG data (2021)

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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)

Accuracy and spatial properties of distributed magnetic source imaging techniques in the investigation of focal epilepsy patients (2021)

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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)

Relative contribution of individual versus combined functional imaging studies in predicting seizure freedom in pediatric epilepsy surgery: an area under the curve analysis (2021)

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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)

Utility of magnetic source imaging in nonlesional focal epilepsy: a prospective study (2021)

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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)

Resting-state functional MRI connectivity impact on epilepsy surgery plan and surgical candidacy: prospective clinical work

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OBJECTIVE The authors' goal was to prospectively quantify the impact of resting-state functional MRI (rs-fMRI) on pediatric epilepsy surgery planning.

METHODS Fifty-one consecutive patients (3 months to 20 years old) with intractable epilepsy underwent rs-fMRI for presurgical evaluation. The team reviewed the following available diagnostic data: video-electroencephalography (n = 51), structural MRI (n = 51), FDG-PET (n = 42), magnetoencephalography (n = 5), and neuropsychological testing (n = 51) results to formulate an initial surgery plan blinded to the rs-fMRI findings. Subsequent to this discussion, the connectivity results were revealed and final recommendations were established. Changes between pre- and post-rs-fMRI treatment plans were determined, and changes in surgery recommendation were compared using McNemar's test.

RESULTS Resting-state fMRI was successfully performed in 50 (98%) of 51 cases and changed the seizure onset zone localization in 44 (88%) of 50 patients. The connectivity results prompted 6 additional studies, eliminated the ordering of 11 further diagnostic studies, and changed the intracranial monitoring plan in 10 cases. The connectivity results significantly altered surgery planning with the addition of 13 surgeries, but it did not eliminate planned surgeries (p = 0.003). Among the 38 epilepsy surgeries performed, the final surgical approach changed due to rs-fMRI findings in 22 cases (58%), including 8 (28%) of 29 in which extraoperative direct electrical stimulation mapping was averted.

CONCLUSIONS This study demonstrates the impact of rs-fMRI connectivity results on the decision-making for pediatric epilepsy surgery by providing new information about the location of eloquent cortex and the seizure onset zone. Additionally, connectivity results may increase the proportion of patients considered eligible for surgery while optimizing the need for further testing.

Keywords: DRE = drug-resistant epilepsy, EEG = electroencephalography, EPCC = epilepsy patient care conference, ICA = independent component analysis, MEG = magnetoencephalography, RNS = responsive neurostimulation, RSN = resting-state network, SOZ = seizure onset zone, VNS = vagus nerve stimulation, connectivity, epilepsy surgery, resting-state functional MRI, rs-fMRI = resting-state functional MRI, seizure, surgical candidacy, surgical technique

Journal of neurosurgery. Pediatrics (2020) (32197251)

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.

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Somatosensory evoked fields predict response to vagus nerve stimulation (2021)

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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 somatosensory 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

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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)

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 dis-concordant MEG results.

Keywords: Drug-resistant epilepsy, Epilepsy surgery, Epileptogenic zone, Magnetoencephalography

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Magnetoencephalography imaging of high frequency oscillations strengthens presurgical localization and outcome prediction (2020)

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ABSTRACT In patients with medically refractory epilepsy, resective surgery is the mainstay of therapy to achieve seizure freedom. However, 20-50% of cases have intractable seizures post-surgery due to the imprecise determination of epileptogenic zone. Recent intracranial studies suggest that high frequency oscillations between 80 and 200 Hz could serve as one of the consistent epileptogenicity biomarkers for localization of the epileptogenic zone. However, these high frequency oscillations are not adopted in the clinical setting because of difficult non-invasive detection. Here, we investigated non-invasive detection and localization of high frequency oscillations and its clinical utility in accurate pre-surgical assessment and post-surgical outcome prediction. We prospectively recruited 52 patients with medically refractory epilepsy who underwent standard pre-surgical workup including magnetoencephalography (MEG) followed by resective surgery after determination of the epileptogenic zone. The post-surgical outcome was assessed after 22.14 ± 10.05 months. Interictal epileptic spikes were expertly identified, and interictal epileptic oscillations across the neural activity frequency spectrum from 8 to 200 Hz were localized using adaptive spatial filtering methods. Localization results were compared with epileptogenic zone and resected cortex for congruence assessment and validated against the clinical outcome. The concordance rate of high frequency oscillations sources (80-200 Hz) with the presumed epileptogenic zone and the resected cortex were 75.0% and 78.8%, respectively, which is superior to that of other frequency bands and standard dipole fitting methods. High frequency oscillation sources corresponding with the resected cortex, had the best sensitivity of 78.0%, positive predictive value of 100% and an accuracy of 78.84% to predict the patient's surgical outcome, among all other frequency bands. If high frequency oscillation sources were spatially congruent with resected cortex, patients had an

odds ratio of 5.67 and 82.4% probability of achieving a favourable surgical outcome. If high frequency oscillations sources were discordant with the epileptogenic zone or resection area, patient has an odds ratio of 0.18 and only 14.3% probability of achieving good outcome, and mostly tended to have an unfavourable outcome ($\chi 2 = 5.22$; $P = 0.02$; $\varphi = -0.317$). In receiver operating characteristic curve analyses, only sources of high-frequency oscillations demonstrated the best sensitivity and specificity profile in determining the patient's surgical outcome with area under the curve of 0.76, whereas other frequency bands indicate a poor predictive performance. Our study is the first non-invasive study to detect high frequency oscillations, address the efficacy of high frequency oscillations over the different neural oscillatory frequencies, localize them and clinically validate them with the post-surgical outcome in patients with medically refractory epilepsy. The evidence presented in the current study supports the fact that HFOs might significantly improve the presurgical assessment, and post-surgical outcome prediction, where it could widely be used in a clinical setting as a non-invasive biomarker.

Keywords: biomarker, high frequency oscillation, magnetoencephalography, ripple, surgical outcome

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Magnetoencephalography for epileptic focus localization in a series of 1000 cases (2020)

Rampp, Stefan; Stefan, Hermann; Wu, Xintong; Kaltenhäuser, Martin; Maess, Burkhard; Schmitt, Friedhelm C; Wolters, Carsten H; Hamer, Hajo; Kasper, Burkhard S; Schwab, Stefan; Doerfler, Arndt; Blümcke, Ingmar; Rössler, Karl; Buchfelder, Michael

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ABSTRACT The aim of epilepsy surgery in patients with focal, pharmacoresistant epilepsies is to remove the complete epileptogenic zone to achieve long-term seizure freedom. In addition to a spectrum of diagnostic methods, magnetoencephalography focus localization is used for planning of epilepsy surgery. We present results from a retrospective observational cohort study of 1000 patients, evaluated using magnetoencephalography at the University Hospital Erlangen over the time span of 28 years. One thousand consecutive cases were included in the study, evaluated at the University Hospital Erlangen between 1990 and 2018. All patients underwent magnetoencephalography as part of clinical workup for epilepsy surgery. Of these, 405 underwent epilepsy surgery after magnetoencephalography, with postsurgical follow-ups of up to 20 years. Sensitivity for interictal epileptic activity was evaluated, in addition to concordance of localization with the consensus of presurgical workup on a lobar level. We evaluate magnetoencephalography characteristics of patients who underwent epilepsy surgery versus patients who did not proceed to surgery. In operated patients, resection of magnetoencephalography localizations were related to postsurgical seizure outcomes, including long-term results after several years. In comparison, association of lesionectomy with seizure outcomes was analysed. Measures of diagnostic accuracy were calculated for magnetoencephalography resection and lesionectomy. Sensitivity for interictal epileptic activity was 72% with significant differences between temporal and extra-temporal lobe epilepsy. Magnetoencephalography was concordant with the presurgical consensus in 51% and showed additional or more focal involvement in an additional 32%. Patients who proceeded to surgery showed a significantly higher percentage of monofocal magnetoencephalography results. Complete magnetoencephalography resection was associated with significantly higher chances to achieve seizure freedom in the short and long-term. Diagnostic accuracy was significant in temporal and extra-temporal lobe cases, but was significantly higher in extra-temporal lobe epilepsy (diagnostic odds ratios of 4.4 and 41.6). Odds

ratios were also higher in non-lesional versus lesional cases (42.0 versus 6.2). The results show that magnetoencephalography provides non-redundant information, which significantly contributes to patient selection, focus localization and ultimately long-term seizure freedom after epilepsy surgery. Specifically in extra-temporal lobe epilepsy and non-lesional cases, magnetoencephalography provides excellent accuracy.

Keywords: epilepsy, epilepsy surgery, long-term outcome, magnetic source imaging, magnetoencephalography

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A network approach to investigate the bi-hemispheric synchrony in absence epilepsy (2020)

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OBJECTIVE Our objective was to unravel the dynamics underlying spike-and-wave discharges (SWDs) characteristic for childhood absence epilepsy.

METHODS SWDs were recorded for a cohort of 28 children using magnetoencephalography. Non-linear association analyses and a graph theoretical metric of local connectedness (LoC) were utilized in a sliding window starting one s before till four s after ictal onset.

RESULTS A focal pattern of bilateral frontal and parietal areas with high LoC during the spikes alternated by generalized patterns during the waves was found for all children studied during generalization of the SWDs. In the interval preceding the generalization a focal parietal region was most often (16/28) encountered and less often an occipital (4/28), temporal (5/28) or frontal (3/28) region. 55% of the children with a parietal/occipital focal onset became seizure free after the administration of two anti-epileptic drugs, and only 12.5% with a temporal/frontal focal onset.

CONCLUSIONS The transition from the interictal to the ictal state is for some of the children characterized by dominant LoC at either the parietal/occipital and for others at the frontal/temporal region.

SIGNIFICANCE The focal onset of the SWDs varies in location among the children with a clinical similar profile, who, however, seemingly are differing with regard to seizure control.

Keywords: Childhood absence epilepsy, Driving sources, Local connectivity mapping, Treatment response

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2019), Vol. 130, No. 9 (31319290)

Synthetic aperture magnetometry and excess kurtosis mapping of Magnetoencephalography (MEG) is predictive of epilepsy surgical outcome in a large pediatric cohort (2020)

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OBJECTIVE Resective surgery is the most effective treatment option for patients with refractory epilepsy; however identification of patients who will benefit from epilepsy surgery remains challenging. Synthetic aperture magnetometry and excess kurtosis mapping (SAM(g2)) of magnetoencephalography (MEG) is a non-invasive tool that warrants further examination in the pediatric epilepsy population. Here, we examined the utility of MEG with SAM(g2) to determine if MEG epileptiform foci correlates with surgical outcome and to develop a predictive model incorporating MEG information to best assess likelihood of seizure improvement/freedom from resective surgery.

METHODS 564 subjects who had MEG at the Children's Hospital of Philadelphia between 2010-2015 were screened. Clinical epilepsy history and prior electrographic records were extracted and reviewed and correlated with MEG findings. MEG assessments were made by both a neurologist and neuroradiologist. Predictive models were developed to assess the utility of MEG in determining Engel class at one year and five years after resective epilepsy surgery.

RESULTS The number of MEG spike foci was highly associated with Engel class outcome at both one year and five years; however, using MEG data in isolation was not significantly predictive of 5 year surgical outcome. When combined with clinical factors; scalp EEG (single ictal onset zone), MRI (lesional or not), age and sex in a logistic regression model MEG foci was significant for Engel class outcome at both 1 year ($p = 0.03$) and 5 years (0.02). The percent correctly classified for Engel class at one year was 78.43% and the positive predictive value was 71.43.

SIGNIFICANCE MEG using SAM(g2) analysis in an important non-invasive tool in the identification of those patients who will benefit most from surgery. Integrating MEG data analysis into pre-surgical evaluation can help to predict epilepsy outcome after resective surgery in the pediatric population if utilized with skilled interpretation.

Keywords: Engel class, Epilepsy surgery, Magnetoencephalography, Pediatric epilepsy, Synthetic aperture magnetometry

Epilepsy research (2019), Vol. 155 (31247475)

Utility of stereo-electroencephalography recording guided by magnetoencephalography in the surgical treatment of epilepsy patients with negative magnetic resonance imaging results (2020)

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ABSTRACT Objective: It is challenging for neurosurgeons to perform surgeries on patients without detectable structural lesions. Therefore, this retrospective study aimed to explore the outcome of stereo-electroencephalography (SEEG) in suspicious areas guided by magnetoencephalography (MEG)-magnetic resonance imaging (MRI) reconstruction in MRI-negative epilepsy patients. Methods: This study included 47 patients with negative-MRI epilepsy. Seizure outcome at 24 months was assessed using a modified Engel's classification. Accordingly, class I and II were considered favorable outcomes, whereas classes III and IV were unfavorable. Furthermore, patients were classified into a consistent group if the results of MEG and SEEG indicated the same area of the brain. The relationship between surgical outcome and the concordance of MEG and SEEG was analyzed. Results: A complete seizure-free condition was achieved in 22 (47%) patients. Sex, handedness, age and duration of illness were not significantly associated with seizure-free outcome ($p = .187$ [Pearson chi-squared test]). The number of patients with favorable outcome (Engle I and II) was as high as 68% at

the time of follow-up. Furthermore, more seizure-free patients were found in the SEEG and MEG consistent group. Conclusions: SEEG is a valuable tool in the pre-evaluation for resective epilepsy surgery, particularly in negative-MRI epilepsy patients; MEG greatly facilitates localization for SEEG electrode implantation. However, none of these tools are absolutely sensitive and reliable; therefore, collecting as much information as possible is necessary to achieve satisfactory results in epilepsy surgery.

Keywords: MEG, SEEG, epilepsy surgery, negative-MRI

The International journal of neuroscience (2019), Vol. 129, No. 11 (31215295)

Automatic diagnosis of neurological diseases using MEG signals with a deep neural network (2020)

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ABSTRACT The application of deep learning to neuroimaging big data will help develop computer-aided diagnosis of neurological diseases. Pattern recognition using deep learning can extract features of neuroimaging signals unique to various neurological diseases, leading to better diagnoses. In this study, we developed MNet, a novel deep neural network to classify multiple neurological diseases using resting-state magnetoencephalography (MEG) signals. We used the MEG signals of 67 healthy subjects, 26 patients with spinal cord injury, and 140 patients with epilepsy to train and test the network using 10-fold cross-validation. The trained MNet succeeded in classifying the healthy subjects and those with the two neurological diseases with an accuracy of 70.7 ± 10.6%, which significantly exceeded the accuracy of 63.4 ± 12.7% calculated from relative powers of six frequency bands (δ: 1-4 Hz; θ: 4-8 Hz; low-α: 8-10 Hz; high-α: 10-13 Hz; β: 13-30 Hz; low-γ: 30-50 Hz) for each channel using a support vector machine as a classifier ($p = 4.2 \times 10[-2]$). The specificity of classification for each disease ranged from 86-94%. Our results suggest that this technique would be useful for developing a classifier that will improve neurological diagnoses and allow high specificity in identifying diseases.

Scientific reports (2019), Vol. 9, No. 1 (30911028)

MEG Assessment of Expressive Language in Children Evaluated for Epilepsy Surgery (2019)

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ABSTRACT Establishing language dominance is an important step in the presurgical evaluation of patients with refractory epilepsy. In the absence of a universally accepted gold-standard non-invasive method to determine language dominance in the preoperative assessment, a range of tools and methodologies have recently received attention. When applied to pediatric age, many of the proposed methods, such as functional magnetic resonance imaging (fMRI), may present some challenges due to the time-varying effects of epileptogenic lesions and of on-going seizures on maturational phenomena. Magnetoencephalography (MEG) has the advantage of being insensitive to the distortive effects of anatomical lesions on brain microvasculature and to differences in the metabolism or vascularization of

the developing brain and also provides a less intimidating recording environment for younger children. In this study we investigated the reliability of lateralized synchronous cortical activation during a verb generation task in a group of 28 children (10 males and 18 females, mean age 12 years) with refractory epilepsy who were evaluated for epilepsy surgery. The verb generation task was associated with significant decreases in beta oscillatory power (13-30 Hz) in frontal and temporal lobes. The MEG data were compared with other available presurgical non-invasive data including cortical stimulation, neuropsychological and fMRI data on language lateralization where available. We found that the lateralization of MEG beta power reduction was concordant with language dominance determined by one or more different assessment methods (i.e. cortical stimulation mapping, neuropsychological, fMRI or post-operative data) in 89% of patients. Our data suggest that qualitative hemispheric differences in task-related changes of spectral power could offer a promising insight into the contribution of dominant and non-dominant hemispheres in language processing and may help to characterize the specialization and lateralization of language processes in children.

Keywords: Beamformers, Children, Epilepsy surgery, Functional mapping, Hemispheric dominance, Language lateralization, Magnetoencephalography

Brain topography (2019), Vol. 32, No. 3 (30895423)

Simultaneous MEG and EEG to detect ripples in people with focal epilepsy (2020)

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OBJECTIVE We studied ripples (80-250 Hz) simultaneously recorded in electroencephalography (EEG) and magnetoencephalography (MEG) to evaluate the differences.

METHODS Simultaneous EEG and MEG were recorded in 30 patients with drug resistant focal epilepsy. Ripples were automatically detected and visually checked in virtual channels throughout the cortex. The number and location of ripples in EEG and MEG were compared to each other and to a region of interest (ROI) defined by clinically available information.

RESULTS Eleven patients showed ripples in both MEG and EEG, 11 only in EEG and one only in MEG. Twenty-four percent of the ripples occurred simultaneously in EEG and MEG, 71% only in EEG, and 5% only in MEG. Three patients without spikes in EEG showed EEG ripples. Ripple localization was concordant with the ROI in 80% of patients with MEG ripples, as opposed to 62% full or partial concordance for EEG ripples. With the optimal threshold for localizing the ROI, sensitivity and specificity were more than 80%.

CONCLUSIONS Ripples in MEG are less frequent but more specific and sensitive for the region of interest than ripples in EEG. Ripples in EEG can exist without spikes in the EEG.

SIGNIFICANCE Ripples in MEG and EEG provide complementary information.

Keywords: Beamforming, Epilepsy surgery, Focal epilepsy, High frequency oscillations, Ripples, Virtual electrodes

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2019), Vol. 130, No. 7 (30871799)

Assessing the localization accuracy and clinical utility of electric and magnetic source imaging in children with epilepsy (2020)

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OBJECTIVE To evaluate the accuracy and clinical utility of conventional 21-channel EEG (conv-EEG), 72-channel high-density EEG (HD-EEG) and 306-channel MEG in localizing interictal epileptiform discharges (IEDs).

METHODS Twenty-four children who underwent epilepsy surgery were studied. IEDs on conv-EEG, HD-EEG, MEG and intracranial EEG (iEEG) were localized using equivalent current dipoles and dynamical statistical parametric mapping (dSPM). We compared the localization error (ELoc) with respect to the ground-truth Irritative Zone (IZ), defined by iEEG sources, between non-invasive modalities and the distance from resection (Dres) between good- (Engel 1) and poor-outcomes. For each patient, we estimated the resection percentage of IED sources and tested whether it predicted outcome.

RESULTS MEG presented lower ELoc than HD-EEG and conv-EEG. For all modalities, Dres was shorter in good-outcome than poor-outcome patients, but only the resection percentage of the ground-truth IZ and MEG-IZ predicted surgical outcome.

CONCLUSIONS MEG localizes the IZ more accurately than conv-EEG and HD-EEG. MSI may help the presurgical evaluation in terms of patient's outcome prediction. The promising clinical value of ESI for both conv-EEG and HD-EEG prompts the use of higher-density EEG-systems to possibly achieve MEG performance.

SIGNIFICANCE Localizing the IZ non-invasively with MSI/ESI facilitates presurgical evaluation and surgical prognosis assessment.

Keywords: EEG, Epilepsy surgery, Intracranial EEG, Irritative zone, Magnetoencephalography, Source localization

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2019), Vol. 130, No. 4 (30771726)

A Magnetoencephalography Study of Pediatric Interictal Neuromagnetic Activity Changes and Brain Network Alterations Caused by Epilepsy in the High Frequency (80-1000 Hz) (2020)

Meng, Lu

ABSTRACT More and more studies propose that high frequency brain signals are promising biomarkers of epileptogenic zone. In this paper, our aim is to investigate the neuromagnetic changes and brain network topological alterations during an interictal period at high frequency ranges (80-1000 Hz) between healthy controls and epileptic patients with Magnetoencephalography. We analyzed neuromagnetic activities with accumulated source imaging, and constructed brain network based on graph theory. Neuromagnetic activity changes and brain network alterations between two groups were analyzed in three frequency bands: ripple (80-250 Hz), fast ripples (FRs, 250-500 Hz), and very high frequency oscillations (VHFO, 500-1000 Hz). We found that epileptic patients showed significantly altered patterns of neuromagnetic source localization and altered brain network patterns. And, we also found that mean functional connectivity and the number of modules from epileptic patients significantly increased in the ripple and FRs bands, and mean clustering coefficient from epileptic patients significantly decreased in the ripple and FRs bands. We also found that the mean functional connectivity was positively correlated with duration of epilepsy in the ripple and VHFO bands, and the number of modules was positively correlated with the duration of epilepsy in the ripple, FRs, and

VHFO bands. Our results indicate that epilepsy can alter patients' neuromagnetic activities and brain networks in the high-frequency ranges, and these alterations become more pathological as the duration of epilepsy grows longer.

IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society (2019), Vol. 27, No. 3 (30762563)

Monaural 40-Hz auditory steady-state magnetic responses can be useful for identifying epileptic focus in mesial temporal lobe epilepsy (2019)

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OBJECTIVE Patients with mesial temporal lobe epilepsy (mTLE) often exhibit central auditory processing (CAP) dysfunction. Monaural 40-Hz auditory steady-state magnetic responses (ASSRs) were recorded to explore the pathophysiology of mTLE.

METHODS Eighteen left mTLE patients, 11 right mTLE patients and 16 healthy controls (HCs) were examined. Monaural clicks were presented at a rate of 40 Hz. Phase-locking factor (PLF) and power values were analyzed within bilateral Heschl's gyri.

RESULTS Monaural 40-Hz ASSR demonstrated temporal frequency dynamics in both PLF and power data. Symmetrical hemispheric contralaterality was revealed in HCs. However, predominant contralaterality was absent in mTLE patients. Specifically, right mTLE patients exhibited a lack of contralaterality in response to left ear but not right ear stimulation, and vice versa in left mTLE patients.

CONCLUSION This is the first study to use monaural 40-Hz ASSR with unilateral mTLE patients to clarify the relationship between CAP and epileptic focus. CAP dysfunction was characterized by a lack of contralaterality corresponding to epileptic focus.

SIGNIFICANCE Monaural 40-Hz ASSR can provide useful information for localizing epileptic focus in mTLE patients.

Keywords: Central auditory processing, Contra-laterality index, Magnetoencephalography, Mesial temporal lobe epilepsy, Monaural auditory steady-state response, Temporal frequency dynamics

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2019), Vol. 130, No. 3 (30669010)

Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study (2019)

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OBJECTIVE To determine the diagnostic accuracy and clinical utility of electromagnetic source imaging (EMSI) in presurgical evaluation of patients with epilepsy.

METHODS We prospectively recorded magnetoencephalography (MEG) simultaneously with EEG and performed EMSI, comprising electric source imaging, magnetic source imaging, and analysis of combined MEG-EEG datasets, using 2 different software packages. As reference standard for irritative zone (IZ) and seizure onset zone (SOZ), we used intracranial recordings and for localization accuracy, outcome 1 year after operation.

RESULTS We included 141 consecutive patients. EMSI showed localized epileptiform discharges in 94 patients (67%). Most of the epileptiform discharge clusters (72%) were identified by both modalities, 15% only by EEG, and 14% only by MEG. Agreement was substantial between inverse solutions and moderate between software packages. EMSI provided new information that changed the management plan in 34% of the patients, and these changes were useful in 80%. Depending on the method, EMSI had a concordance of 53% to 89% with IZ and 35% to 73% with SOZ. Localization accuracy of EMSI was between 44% and 57%, which was not significantly different from MRI (49%-76%) and PET (54%-85%). Combined EMSI achieved significantly higher odds ratio compared to electric source imaging and magnetic source imaging.

CONCLUSION EMSI has accuracy similar to established imaging methods and provides clinically useful, new information in 34% of the patients.

CLASSIFICATION OF EVIDENCE This study provides Class IV evidence that EMSI had a concordance of 53%-89% and 35%-73% (depending on analysis) for the localization of epileptic focus as compared with intracranial recordings-IZ and SOZ, respectively.

Neurology (2019), Vol. 92, No. 6 (30610090)

Magnetoencephalography as a Prognostic Tool in Patients with Medically Intractable Temporal Lobe Epilepsy (2019)

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BACKGROUND Most surgical treatments for medically intractable temporal lobe epilepsy are helpful. When a patient has persistent symptoms after surgery, there are no tests that accurately predict whether a patient will have remnant epileptic foci. The aim of this study was to evaluate the usefulness of magnetoencephalography (MEG) as a prognostic tool in patients with temporal lobe epilepsy.

METHODS From July 2012 to July 2016, 21 patients underwent preoperative and postoperative MEG at our center. Postoperative MEG was performed within 2 weeks after surgery. We analyzed MEG by estimating the time-frequency component of the signal to define gamma oscillations (GOs), which are an indicator of epileptogenic foci. We analyzed the relationship between GOs on MEG and surgical outcomes.

RESULTS Mean follow-up period was 28.3 months (range, 13-44 months). At the last follow-up visit, patients were divided into 2 groups according to surgical outcome. All patients showed spike waves and GOs on preoperative electroencephalography and MEG. In the seizure control group (16 patients), spike waves (2 patients) and GOs (2 patients) were seen postoperatively despite absence of symptoms. In the recurrent seizure group (5 patients), whereas 3 patients showed spike waves, all 5 patients showed GOs on MEG postoperatively. There was a significant association between

presence of GOs on postoperative MEG and surgical outcome (P = 0.01).

CONCLUSIONS MEG can provide valuable postsurgical information on epileptic foci in patients with recurrent symptoms; GOs on postoperative MEG were especially correlated with epileptic recurrence. Our data show that GOs on postoperative MEG may have prognostic value.

Keywords: Anterior temporal lobectomy, Magnetoencephalography, Prognosis, Temporal lobe epilepsy

World neurosurgery (2019), Vol. 123 (30579026)

MRI, Magnetoencephalography, and Surgical Outcome of Oligodendrocytosis versus Focal Cortical Dysplasia Type I (2019)

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BACKGROUND AND PURPOSE Abnormalities of oligodendrocytes have been reported in surgical specimens of patients with medically intractable epilepsy. The aim of this study was to compare the MR imaging, magnetoencephalography, and surgical outcome of children with oligodendrocytosis relative to focal cortical dysplasia I.

MATERIALS AND METHODS Oligodendrocytosis included oligodendroglial hyperplasia, oligodendrogliosis, and oligodendroglial-like cells in the white matter, gray matter, or both from children with medically intractable epilepsy. Focal cortical dysplasia I included radial and tangential cortical dyslamination. The MR imaging, magnetoencephalography, type of operation, location, and seizure outcome of oligodendrocytosis, focal cortical dysplasia I, and oligodendrocytosis + focal cortical dysplasia I were compared.

RESULTS Eighteen subjects (39.1%) had oligodendrocytosis, 21 (45.7%) had focal cortical dysplasia I, and 7 (15.2%) had oligodendrocytosis + focal cortical dysplasia I. There were no significant differences in the type of seizures, focal or nonfocal epileptiform discharges, magnetoencephalography, and MR imaging features, including high T1 signal in the cortex, high T2/FLAIR signal in the cortex or subcortical white matter, increased cortical thickness, blurring of the gray-white junction, or abnormal sulcation and gyration among those with oligodendrocytosis, focal cortical dysplasia I, or oligodendrocytosis + focal cortical dysplasia I (P > .01). There were no significant differences in the extent of resection (unilobar versus multilobar versus hemispherectomy), location of the operation (temporal versus extratemporal versus both), or seizure-free outcome of oligodendrocytosis, focal cortical dysplasia I, and oligodendrocytosis + focal cortical dysplasia I (P > .05).

CONCLUSIONS Oligodendrocytosis shared MR imaging and magnetoencephalography features with focal cortical dysplasia I, and multilobar resection was frequently required to achieve seizure freedom. In 15% of cases, concurrent oligodendrocytosis and focal cortical dysplasia I were identified. The findings suggest that oligodendrocytosis may represent a mild spectrum of malformations of cortical development.

AJNR. American journal of neuroradiology (2018), Vol. 39, No. 12 (30442696)

Detection and localization of interictal ripples with magnetoencephalography in the presurgical evaluation of drug-resistant insular epilepsy (2020)

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ABSTRACT Precise noninvasive presurgical localization of insular epilepsy is important. The objective of the present study was to detect and localize interictal high-frequency oscillations (HFOs) in patients with insular epilepsy at the source levels using magnetoencephalography (MEG). We investigated whether HFOs can delineate epileptogenic areas. We analysed MEG data with new accumulated source imaging (HFOs, 80-250 Hz ripples during spikes) and conventional dipole modelling (spikes) methods for localizing epileptic foci. We evaluated the relationship of the resection of focal brain regions containing interictal HFOs and the spikes with the postsurgical seizure outcome. Interictal HFOs were localized in the insular epileptogenic zone (EZ) in 18 out of 21 patients undergoing surgical treatment for clinically diagnosed insular epilepsy. While dipole clusters of spikes were involved in the insular EZ in 15 patients. Both the HFOs and the dipole cluster were localized in the insula in 14 patients. The seizure-free percentage was 87% for the resection of brain regions generating HFOs, whereas 80% for the resection of brain regions generating spikes. There was a much higher chance of freedom from seizures with complete resection of the HFO-generating regions than with partial resection or no resection (P = 0.031). No such difference was seen for spike-generating regions. Our results suggest that HFOs from insular epilepsy could be noninvasively detected and quantitatively assessed with MEG technology. MEG HFOs (ripples during spikes) may be valuable for the localization of the epileptogenic zone in insular epilepsy.

Keywords: High-frequency oscillations, Insular epilepsy, Magnetoencephalography, Seizure

Brain research (2019), Vol. 1706 (30408475)

Ictal Source Locations and Cortico-Thalamic Connectivity in Childhood Absence Epilepsy: Associations with Treatment Response (2019)

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ABSTRACT Childhood absence epilepsy (CAE), the most common pediatric epilepsy syndrome, is usually treated with valproic acid (VPA) and lamotrigine (LTG) in China. This study aimed to investigate the ictal source locations and functional connectivity (FC) networks between the cortices and thalamus that are related to treatment response. Magnetoencephalography (MEG) data from 25 patients with CAE were recorded at 300 Hz and analyzed in 1-30 Hz frequency bands. Neuromagnetic sources were volumetrically scanned with accumulated source imaging. The FC networks between the cortices and thalamus were evaluated at the source level through a connectivity analysis. Treatment outcome was assessed after 36-66 months following MEG recording. The children with CAE were divided into LTG responder, LTG non-responder, VPA responder and VPA non-responder groups. The ictal source locations and cortico-thalamic FC networks were compared to the treatment response. The ictal source locations in the post-dorsal medial frontal cortex (post-DMFC, including the medial primary motor cortex and the supplementary sensorimotor area) were observed in all LTG non-responders but in all LTG responders. At 1-7 Hz, patients with fronto-thalamo-parietal/occipital (F-

T-P/O) networks were older than those with fronto-thalamic (F-T) networks or other cortico-thalamic networks ($p = 0.000$). The duration of seizures in patients with F-T-P/O networks at 1-7 Hz was longer than that in patients with F-T networks or other cortico-thalamic networks ($p = 0.001$). The ictal post-DMFC source localizations suggest that children with CAE might experience initial LTG monotherapy failure. Moreover, the cortico-thalamo-cortical network is associated with age. Finally, the cortico-thalamo-cortical network consists of anterior and posterior cortices and might contribute to the maintenance of discharges.

Keywords: Childhood absence epilepsy, Cortico–thalamic network, Magnetoencephalography, Source location, Treatment response

Brain topography (2019), Vol. 32, No. 1 (30291582)

Relative Yield of MEG and EEG Spikes in Simultaneous Recordings (2018)

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PURPOSE Most clinical magnetoencephalography (MEG) centers record both MEG and EEG, but model only MEG sources. This may be related to the belief that MEG spikes are more prevalent, MEG is more sensitive, or to proprietary software limitations. Biophysics would contend, however, that EEG, being sensitive to radial and tangential source orientations, would provide complementary data for analysis.

METHODS We recorded 306 channels of MEG and 25 channels of EEG simultaneously in 297 consecutive patients over 3 years. We inspected the MEG and EEG recordings separately, identified spikes in both, determined whether their voltage and/or magnetometer magnetic fields were dipolar and thus model-worthy, and segregated them into types based on similar and distinct field topography. We placed for each patient their spike types into categories, including those with both a recognizable MEG and EEG signal and those with only an MEG and only an EEG signal.

RESULTS Eighty-three percent of patients had spikes recorded, and these patients had an average of 2.7 spike types each. Fifty-six percent of spike types were present in both MEG and EEG. However, 36% of spike types were only evident in EEG, whereas 8% were noted in MEG alone. In 49% of patients with spikes, MEG review missed at least one spike type, whereas in 17% of patients, EEG review missed at least one spike type.

CONCLUSIONS To obtain an optimal yield of diagnostic information, EEG should also be subjected to source analysis in any clinical MEG study. EEG and MEG data are indeed complementary.

Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society (2018), Vol. 35, No. 6 (30234690)

Magnetoencephalographic Recordings in Infants: A Retrospective Analysis of Seizure-Focus Yield and Postsurgical Outcomes (2018)

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PURPOSE Magnetoencephalography (MEG) is often incorporated into the presurgical work-up of children with pharmacoresistant epilepsy. There is growing literature on its role in improving selection for epilepsy surgery, particularly when brain MRI is "non-lesional" or in patients with recurrence or intractable seizures after epilepsy surgery. There are, however, no reports on the extrapolation of its role in the presurgical decision-making process of infants.

METHODS We performed a retrospective analysis of infants who underwent MEG over a 10-year period

at our center for presurgical work-up. We reviewed medical records to ascertain seizure history, work-up procedures including brain MRI and scalp EEG, and in the case of surgery, intracranial recordings, operative notes, and follow-up outcomes.

RESULTS We identified 31 infants (<2 years of age) who underwent MEG recordings. Despite EEG interictal readings showing patterns of generalized dysfunction in 80%, MEG was able to pinpoint the foci of epileptic activity in 45%. In the MRI-negative group, 44% had focal lateralized interictal spikes on MEG. The sensitivity of MEG to detect interictal epileptiform activity was 90%, and its ability to provide additional information was 28%. Among 18 infants who had surgery, 13 became seizure free at follow-up. The percentage of infants with a focal spike volume on MEG studies and a seizure-free outcome was 66%.

CONCLUSIONS MEG recordings in infants were found to be as sensitive for identifying seizure focus as other age groups, also supplying additional information to the decision-making process and validating its role in the presurgical work-up of infants with intractable epilepsy.

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Predicting seizure outcome of vagus nerve stimulation using MEG-based network topology (2019)

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ABSTRACT Vagus nerve stimulation (VNS) is a low-risk surgical option for patients with drug resistant epilepsy, although it is impossible to predict which patients may respond to VNS treatment. Resting-state magnetoencephalography (rs-MEG) connectivity analysis has been increasingly utilized to investigate the impact of epilepsy on brain networks and identify alteration of these networks after different treatments; however, there is no study to date utilizing this modality to predict the efficacy of VNS treatment. We investigated whether the rs-MEG network topology before VNS implantation can be used to predict efficacy of VNS treatment. Twenty-three patients with epilepsy who had MEG before VNS implantation were included in this study. We also included 89 healthy control subjects from the Human Connectome Project. Using the phase-locking value in the theta, alpha, and beta frequency bands as a measure of rs-MEG functional connectivity, we calculated three global graph measures: modularity, transitivity, and characteristic path length (CPL). Our results revealed that the rs-MEG graph measures were significantly heritable and had an overall good test-retest reliability, and thus these measures may be used as potential biomarkers of the network topology. We found that the modularity and transitivity in VNS responders were significantly larger and smaller, respectively, than those observed in VNS non-responders. We also observed that the modularity and transitivity in three frequency bands and CPL in delta and beta bands were significantly different in controls than those found in responders or non-responders, although the values of the graph measures in controls were closer to those of responders than non-responders. We used the modularity and transitivity as input features of a naïve Bayes classifier, and achieved an accuracy of 87% in classification of non-responders, responders, and controls. The results of this study revealed that MEG-based graph measures are reliable biomarkers, and that these measures may be used to predict seizure outcome of VNS treatment.

Keywords: Functional connectivity, Graph measures, Human connectome project (HCP), Magnetoencephalography (MEG), Phase-locking value (PLV), Seizure outcome, VNS efficacy, Vagus nerve stimulation (VNS)

NeuroImage. Clinical (2018), Vol. 19 (30003036)

Coregistrating magnetic source and magnetic resonance imaging for epilepsy surgery in focal cortical dysplasia (2019)

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BACKGROUND Epilepsy surgery for focal cortical dysplasia type II (FCD II) offers good chances for seizure freedom, but remains a challenge with respect to lesion detection, defining the epileptogenic zone and the optimal resection strategy. Integrating results from magnetic source imaging from magnetoencephalography (MEG) with magnetic resonance imaging (MRI) including MRI postprocessing may be useful for optimizing these goals.

METHODS We here present data from 21 adult FCD II patients, investigated during a 10 year period and evaluated including magnetic source imaging. 16 patients had epilepsy surgery, i.e. histopathologically verified FCD II, and a long follow up. We present our analysis of epileptogenic zones including MEG in relation to structural data according to MRI data and relate these results to surgical outcomes.

RESULTS FCD II in our cohort was characterized by high MEG yield and localization accuracy and MEG showed impact on surgical success-rates. MEG source localizations were detected in 95.2% of patients and were as close as 12.3 ± 8,1 mm to the MRI-lesion. After a mean follow up of >3 years, we saw >80% Engel I outcomes, with more favourable outcomes when the MEG source was completely resected (Fishers exact test 0,033).

CONCLUSION We argue for a high value of conducting a combined MEG-MRI approach in the presurgical

workup and the resection strategy in patients with FCD II related epilepsy.

Keywords: Focal cortical dysplasia, Magnetic source imaging, epilepsy surgery

NeuroImage. Clinical (2018), Vol. 19 (29984157)

Magnetoencephalography and ictal SPECT in patients with failed epilepsy surgery (2019)

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OBJECTIVE Selected patients with intractable focal epilepsy who have failed a previous epilepsy surgery can become seizure-free with reoperation. Preoperative evaluation is exceedingly challenging in this cohort. We aim to investigate the diagnostic value of two noninvasive approaches, magnetoencephalography (MEG) and ictal single-photon emission computed tomography (SPECT), in patients with failed epilepsy surgery.

METHODS We retrospectively included a consecutive cohort of patients who failed prior resective epilepsy surgery, underwent re-evaluation including MEG and ictal SPECT, and had another surgery after the re-evaluation. The relationship between resection and localization from each test was determined, and their association with seizure outcomes was analyzed.

RESULTS A total of 46 patients were included; 21 (46%) were seizure-free at 1-year followup after reoperation. Twenty-seven (58%) had a positive MEG and 31 (67%) had a positive ictal SPECT. The resection of MEG foci was significantly associated with seizure-free outcome ($p = 0.002$). Overlap of ictal SPECT hyperperfusion zones with resection was significantly associated with seizure-free outcome in the subgroup of patients with injection time ≤20 seconds($p = 0.03$), but did not show significant association in the overall cohort ($p = 0.46$) although all injections were ictal. Patients whose MEG and ictal SPECT were concordant on a sublobar level had a significantly higher chance of seizure freedom ($p = 0.05$).

CONCLUSIONS MEG alone achieved successful localization in patients with failed epilepsy surgery with a statistical significance. Only ictal SPECT with early injection (≤20 seconds) had good localization value. Sublobar concordance between both tests was significantly associated with seizure freedom. SPECT can provide essential information in MEG-negative cases and vice versa.

SIGNIFICANCE Our results emphasize the importance of considering a multimodal presurgical evaluation including MEG and SPECT in all patients with a previous failed epilepsy surgery.

Keywords: Epilepsy, Failed surgery, MEG, SPECT

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Assessment of the Utility of Ictal Magnetoencephalography in the Localization of the Epileptic Seizure Onset Zone (2019)

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IMPORTANCE Literature on ictal magnetoencephalography (MEG) in clinical practice and the relationship to other modalities is limited because of the brevity of routine studies.

OBJECTIVE To investigate the utility and reliability of ictal MEG in the localization of the epileptogenic zone.

DESIGN, SETTING, AND PARTICIPANTS A retrospective medical record review and prospective analysis of a novel ictal rhythm analysis method was conducted at a tertiary epilepsy center with a wide base of referrals for epilepsy surgery evaluation and included consecutive cases of patients who experienced epileptic seizures during routine MEG studies from March 2008 to February 2012. A total of 377 studies screened. Data were analyzed from November 2011 to October 2015.

MAIN OUTCOMES AND MEASURES Presurgical workup and interictal and ictal MEG data were reviewed. The localizing value of using extended-source localization of a narrow band identified visually at onset was analyzed.

RESULTS Of the 44 included patients, the mean (SD) age at the time of recording was 19.3 (14.9) years, and 25 (57%) were male. The mean duration of recording was 51.2 minutes. Seizures were provoked by known triggers in 3 patients and were spontaneous otherwise. Twenty-five patients (57%) had 1 seizure, 6 (14%) had 2, and 13 (30%) had 3 or more. Magnetoencephalography single equivalent current dipole analysis was possible in 29 patients (66%), of whom 8 (28%) had no clear interictal discharges. Sublobar concordance between ictal and interictal dipoles was seen in 18 of 21 patients (86%). Three patients (7%) showed clear ictal MEG patterns without electroencephalography changes. Ictal MEG dipoles correlated with the lobe of onset in 7 of 8 patients (88%) who underwent intracranial electroencephalography evaluations. Reasons for failure to identify ictal dipoles included diffuse or poor dipolar ictal patterns, no MEG changes, and movement artifact. Resection of areas containing a minimum-norm estimate of a narrow band at onset, not single equivalent current dipole, was associated with sustained seizure freedom.

CONCLUSIONS AND SIGNIFICANCE Ictal MEG data can provide reliable localization, including in cases that are difficult to localize by other modalities. These findings support the use of extended-source localization for seizures recorded during MEG.

JAMA neurology (2018), Vol. 75, No. 10 (29889930)

Increased Functional MEG Connectivity as a Hallmark of MRI-Negative Focal and Generalized Epilepsy (2019)

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ABSTRACT Epilepsy is one of the most prevalent neurological diseases with a high morbidity. Accumulating evidence has shown that epilepsy is an archetypical neural network disorder. Here we developed a non-invasive cortical functional connectivity analysis based on magnetoencephalography (MEG) to assess commonalities and differences in the network phenotype in different epilepsy syndromes (non-lesional/cryptogenic focal and idiopathic/genetic generalized epilepsy). Thirty-seven epilepsy patients with normal structural brain anatomy underwent a 30-min resting state MEG measurement with eyes closed. We only analyzed interictal epochs without epileptiform discharges. The imaginary part of coherency was calculated as an indicator of cortical functional connectivity in five classical frequency bands. This connectivity measure was computed between all sources on individually reconstructed cortical surfaces that were surface-aligned to a common template. In comparison to healthy controls, both focal and generalized epilepsy patients showed widespread increased functional connectivity in several frequency bands, demonstrating the potential of elevated functional connectivity as a common pathophysiological hallmark in different epilepsy types. Furthermore, the comparison between focal and generalized epilepsies revealed increased network con-

nectivity in bilateral mesio-frontal and motor regions specifically for the generalized epilepsy patients. Our study indicated that the surface-based normalization of MEG sources of individual brains enables the comparison of imaging findings across subjects and groups on a united platform, which leads to a straightforward and effective disclosure of pathological network characteristics in epilepsy. This approach may allow for the definition of more specific markers of different epilepsy syndromes, and increased MEG-based resting-state functional connectivity seems to be a common feature in MRI-negative epilepsy syndromes.

Keywords: Graph theory, Imaginary part of coherency, Interictal, Resting state, Whole brain

Brain topography (2018), Vol. 31, No. 5 (29766384)

Magnetoencephalographic Spike Analysis in Patients With Focal Cortical Dysplasia: What Defines a "Dipole Cluster"? (2019)

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BACKGROUND The purpose of this study is to clarify the source distribution patterns of magnetoencephalographic spikes correlated with postsurgical seizure-free outcome in pediatric patients with focal cortical dysplasia.

PATIENTS AND METHODS Thirty-two patients with pathologically confirmed focal cortical dysplasia were divided into seizure-free and seizure-persistent groups according to their surgical outcomes based on Engel classification. In each patient, presurgical magnetoencephalography was reviewed. Dipole sources of magnetoencephalographic spikes were calculated according to a single dipole model. We obtained the following quantitative indices for evaluating dipole distribution: maximum distance over all pairs of dipoles, standard deviation of the distances between each dipole and the mean coordinate of all dipoles, average nearest neighbor distance, the rate of dipoles located within 10, 20, and 30 mm from the mean coordinate, and the rate of dipoles included in the resection. These indices were compared between the two patient groups.

RESULTS Average nearest neighbor distance was significantly smaller in the seizure-free group than in the seizure-persistent group (P = 0.008). The rates of dipoles located within 10, 20, and 30 mm from the mean coordinate were significantly higher in the seizure-free group (P = 0.001, 0.001, 0.005, respectively). The maximum distance, standard deviation, and resection rate of dipoles did not show a significant difference between the two groups.

CONCLUSIONS A spatially restricted dipole distribution of magnetoencephalographic spikes is correlated with postsurgical seizure-free outcomes in patients with focal cortical dysplasia. The distribution can be assessed by quantitative indices that are clinically useful in the presurgical evaluation of these patients.

Keywords: Epilepsy surgery, Equivalent current dipole, Focal cortical dysplasia, Magnetoencephalography, Source localization

Pediatric neurology (2018), Vol. 83 (29685607)

An evaluation of kurtosis beamforming in magnetoencephalography to localize the epileptogenic zone in drug resistant epilepsy patients (2019)

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OBJECTIVE Kurtosis beamforming is a useful technique for analysing magnetoencephalograpy (MEG) data containing epileptic spikes. However, the implementation varies and few studies measure concordance with subsequently resected areas. We evaluated kurtosis beamforming as a means of localizing spikes in drug-resistant epilepsy patients.

METHODS We retrospectively applied kurtosis beamforming to MEG recordings of 22 epilepsy patients that had previously been analysed using equivalent current dipole (ECD) fitting. Virtual electrodes were placed in the kurtosis volumetric peaks and visually inspected to select a candidate source. The candidate sources were compared to the ECD localizations and resection areas.

RESULTS The kurtosis beamformer produced interpretable localizations in 18/22 patients, of which the candidate source coincided with the resection lobe in 9/13 seizure-free patients and in 3/5 patients with persistent seizures. The sublobar accuracy of the kurtosis beamformer with respect to the resection zone was higher than ECD (56% and 50%, respectively), however, ECD resulted in a higher lobar accuracy (75%, 67%).

CONCLUSIONS Kurtosis beamforming may provide additional value when spikes are not clearly discernible on the sensors and support ECD localizations when dipoles are scattered.

SIGNIFICANCE Kurtosis beamforming should be integrated with existing clinical protocols to assist in localizing the epileptogenic zone.

Keywords: Beamforming, Epilepsy, Kurtosis, MEG, Neuroimaging

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Utility of additional dedicated high-resolution 3T MRI in children with medically refractory focal epilepsy (2019)

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PURPOSE In patients with medically refractory epilepsy and normal magnetic resonance imaging (MRI), high-resolution dedicated MRI may identify cryptic lesions. The aim of this study was to assess improvement in lesion detection and its impact on clinical management, using additional high-resolution dedicated 3T MRI in children with medically refractory epilepsy who had normal 3T epilepsy protocol MRI.

MATERIALS AND METHODS Children who had resective epilepsy surgery and suspected focal cortical dysplasia (FCD) or normal 3T epilepsy protocol MRI were included. Those with other diagnosis on MRI including tumor and hippocampal sclerosis were excluded. Patients who had normal MRI on 3T epilepsy protocol underwent dedicated high-resolution 3T MRI through the epileptogenic zone, guided by video EEG, Magnetoencephalography and FDG-PET data.

RESULTS 101 patients with at least 1 year follow-up were included. Twenty-nine of 44 (66%) patients who had normal epilepsy protocol MRI had a lesion identified on dedicated high-resolution MRI. The addition

of dedicated high-resolution MRI to standard epilepsy protocol increased sensitivity from 53.1% (95%CI: 40%-66%) to 85.9% (95%CI: 75%-93%). Identified lesions were concordant to surgical resection in all patients and guided depth/strip electrode insertion in 20/25 (80%) patients who underwent staged resection. Dedicated MRI detected small deep seated lesions in 10/20 (50%), and guided depth electrodes placement, without which it would not be feasible, as the lobar location of epileptogenic zone from other non-invasive tests were not sufficiently precise.

CONCLUSION Patients with non-lesional epilepsy on standard epilepsy protocol MR may benefit from high-resolution dedicated MRI to aid identification of an underlying lesion, which could impact surgical management and improve seizure control.

Keywords: 3T MRI, Diagnostic efficacy, Pediatric refractory epilepsy, Seizure freedom

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Ictal and interictal MEG in pediatric patients with tuberous sclerosis and drug resistant epilepsy (2019)

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PURPOSE Drug resistant epilepsy (DRE) is common in patients with tuberous sclerosis (TS). Interictal MEG has been shown as a valuable instrument in the presurgical workup. The goal of our study was to evaluate the role of ictal MEG in epileptogenic tuber selection, especially in patients with multiple irritative zones.

METHODS The clinical and MEG data of 23 patients with TS and DRE from two medical/research centers were reviewed. Seven pediatric patients, who had seizures during MEG recording and underwent resection or disconnection surgery, were included into the study. Cortical sources of ictal and interictal epileptiform MEG discharges were compared with epileptogenic zone location in six patients with favorable surgery outcome.

RESULTS In patients who improved substantially after surgery all resected and several other tubers demonstrated epileptiform activity on interictal MEG. Ictal MEG provided crucial information about lobar location of the seizure onset zone (SOZ) in two cases, and in the other four it confirmed the SOZ location derived from the interictal data. In one case, ictal MEG findings were unreliable. In one patient, who did not benefit from surgical treatment, the resected tubers did not overlap with interictal and ictal MEG sources.

CONCLUSION The combination of interictal and ictal MEG is a valuable tool for identification of the epileptogenic tuber/tubers in presurgical work-up in patients with TS.

Keywords: Epilepsy surgery, Ictal and interictal MEG, Tuberous sclerosis

Epilepsy research (2018), Vol. 140 (29367178)

Strong coupling between slow oscillations and wide fast ripples in children with epileptic spasms: Investigation of modulation index and occurrence rate (2018)

Iimura, Yasushi; Jones, Kevin; Takada, Lynne; Shimizu, Itsuki; Koyama, Misaki; Hattori, Kyoko; Okazawa, Yushi; Nonoda, Yutaka; Asano, Eishi; Akiyama, Tomoyuki; Go, Cristina; Ochi, Ayako; Snead, O Carter; Donner, Elizabeth J; Rutka, James T; Drake, James M; Otsubo, Hiroshi

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OBJECTIVE Epileptic spasms (ES) often become drug-resistant. To reveal the electrophysiological difference between children with ES (ES+) and without ES (ES-), we compared the occurrence rate (OR) of high-frequency oscillations (HFOs) and the modulation index (MI) of coupling between slow and fast oscillations. In ES+, we hypothesized that (1) pathological HFOs are more widely distributed and (2) slow oscillations show stronger coupling with pathological HFOs than in ES-.

METHODS We retrospectively reviewed 24 children with drug-resistant multilobar onset epilepsy, who underwent intracranial video electroencephalography prior to multilobar resections. We measured the OR of HFOs and determined the electrodes with a high rate of HFOs by cluster analysis. We calculated MI, which reflects the degree of coupling between HFO (ripple/fast ripple [FR]) amplitude and 5 different frequency bands of delta and theta activities (0.5-1 Hz, 1-2 Hz, 2-3 Hz, 3-4 Hz, 4-8 Hz).

RESULTS In ES+ (n = 10), the OR(FRs) , the number of electrodes with high-rate FRs, and the MI(FRs & 3-4 Hz) in all electrodes were significantly higher than in ES- (n = 14). In both the ES+ and ES- groups, MI(ripples/FRs & 3-4 Hz) was the highest among the 5 frequency bands. Within the good seizure outcome group, the OR(FRs) and the MI(FRs & 3-4 Hz) in the resected area in ES+ were significantly higher than in ES- (OR[FRs] , P = .04; MI[FRs & 3-4 Hz] , P = .04).

SIGNIFICANCE In ES+, the larger number of high-rate FR electrodes indicates more widespread epileptogenicity than in ES-. High values of OR(FRs) and MI(FRs & 3-4 Hz) in ES+ compared to ES- are a signature of the severity of epileptogenicity. We proved that ES+ children who achieved seizure freedom following multilobar resections exhibited strong coupling between slow oscillations and FRs.

Keywords: drug-resistant epilepsy, epilepsy surgery, focal seizure, intracranial EEG, multilobar resection

Epilepsia (2018), Vol. 59, No. 3 (29315516)

The clinical impact of integration of magnetoencephalography in the presurgical workup for refractory nonlesional epilepsy (2018)

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OBJECTIVE For patients with nonlesional refractory focal epilepsy (NLRFE), localization of the epileptogenic zone is more arduous, and intracranial electroencephalography (EEG) (icEEG) is frequently required. Planning for icEEG is dependent on combined data from multiple noninvasive modalities. We report the negative impact of lack of integration of magnetoencephalography (MEG) in the presurgical workup in NLRFE.

METHODS Observational MEG case series involving 31 consecutive patients with NLRFE in an academic

epilepsy center. For various reasons, MEG data were not analyzed in a timely manner to be included in the decision-making process. The presumed impact of MEG was assessed retrospectively.

RESULTS Magnetoencephalography would have changed the initial management in 21/31 (68%) had MEG results been available by reducing the number of intracranial electrodes, modifying their position, allowing for direct surgery, canceling the intracranial study, or providing enough evidence to justify one. Good surgical outcome was achieved in 11 out of 17 patients who proceeded to epilepsy surgery. Nine out of eleven had MEG clusters corresponding to the resection area, and MEG findings would have allowed for direct surgery (avoiding icEEG) in 2/11. Six patients had poor outcome including three patients where MEG would have significantly changed the outcome by modifying the resection margin. Magnetoencephalography provided superior information in 3 patients where inadequate coverage precluded accurate mapping of the epileptogenic zone.

CONCLUSION In this single center retrospective study, MEG would have changed patient management, icEEG planning, and surgical outcome in a significant percentage of patients with NLRFE and should be considered in the presurgical workup in those patients.

Keywords: Epilepsy, Magnetoencephalograpy, Nonlesional, Refractory

Epilepsy & behavior: E&B (2018), Vol. 79 (29253675)

Source analysis of epileptiform discharges in absence epilepsy using Magnetoencephalography (MEG) (2019)

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PURPOSE Magnetoencephalography (MEG) was used to record and localize the sources of the epileptiform discharges, in absence epilepsy, at three different time intervals to infer the sources of involvement during generation and propagation.

METHODS Twenty patients with absence epilepsy (M:F=1:1; age: 10.2±3.4years), which included 12 patients with childhood absence epilepsy (CAE) and 8 patients with juvenile absence epilepsy (JAE), were recruited in this prospective MEG based study. MEG epileptiform discharges were divided into three subgroups based on the duration viz., 1s (very short),>1-9.9s (short) and ≥10s (long) and the discharges of each group were averaged independently in each patient. MEG source analysis was performed on these averaged discharges, of each of the subgroups, at the onset, during middle and offset.

RESULTS The source locations obtained, in lobar and gyri levels, were compared across these three groups of varying duration of discharges and in the CAE and JAE subjects. It was observed that the most frequent location of sources from the sublobar, limbic and frontal lobes in all the discharge groups at different time intervals. Also, it was noted that there were only subtle and variable degree of the differences of source localization of epileptic discharges among CAE and JAE subgroups.

CONCLUSION The study provided novel findings regarding origin and propagation of sources of epileptiform discharges in patients with childhood and juvenile absence epilepsies. Such analysis further improves the understanding of network involvement of subcortical and cortical regions in these patients.

Keywords: Absence epilepsy, CAE, Epileptiform discharges, JAE, MEG, Source analysis

Epilepsy research (2018), Vol. 140 (29232569)

Reproducibility of EEG-MEG fusion source analysis of interictal spikes: Relevance in presurgical evaluation of epilepsy (2018)

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ABSTRACT Fusion of electroencephalography (EEG) and magnetoencephalography (MEG) data using maximum entropy on the mean method (MEM-fusion) takes advantage of the complementarities between EEG and MEG to improve localization accuracy. Simulation studies demonstrated MEM-fusion to be robust especially in noisy conditions such as single spike source localizations (SSSL). Our objective was to assess the reliability of SSSL using MEM-fusion on clinical data. We proposed to cluster SSSL results to find the most reliable and consistent source map from the reconstructed sources, the so-called consensus map. Thirty-four types of interictal epileptic discharges (IEDs) were analyzed from 26 patients with well-defined epileptogenic focus. SSSLs were performed on EEG, MEG, and fusion data and consensus maps were estimated using hierarchical clustering. Qualitative (spike-to-spike reproducibility rate, SSR) and quantitative (localization error and spatial dispersion) assessments were performed using the epileptogenic focus as clinical reference. Fusion SSSL provided significantly better results than EEG or MEG alone. Fusion found at least one cluster concordant with the clinical reference in all cases. This concordant cluster was always the one involving the highest number of spikes. Fusion yielded highest reproducibility (SSR EEG = 55%, MEG = 71%, fusion = 90%) and lowest localization error. Also, using only few channels from either modality (21EEG + 272MEG or 54EEG + 25MEG) was sufficient to reach accurate fusion. MEM-fusion with consensus map approach provides an objective way of finding the most reliable and concordant generators of IEDs. We, therefore, suggest the pertinence of SSSL using MEM-fusion as a valuable clinical tool for presurgical evaluation of epilepsy.

Keywords: coherent maximum entropy on the mean, fusion of EEG and MEG, interictal epileptic spikes, presurgical evaluation of epilepsy, reproducibility, single trial localization

Human brain mapping (2018), Vol. 39, No. 2 (29164737)

Magnetoencephalographic imaging of ictal high-frequency oscillations (80-200 Hz) in pharmacologically resistant focal epilepsy (2018)

Velmurugan, Jayabal; Nagarajan, Srikantan S; Mariyappa, Narayanan; Ravi, Shankar G; Thennarasu, Kandavel; Mundlamuri, Ravindranadh C; Raghavendra, Kenchaiah; Bharath, Rose Dawn; Saini, Jitender; Arivazhagan, Arimappamagan; Rajan, Jamuna; Mahadevan, Anita; Rao, Malla B; Satishchandra, Parthasarathy; Sinha, Sanjib

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OBJECTIVE Specificity of ictal high-frequency oscillations (HFOs) in identifying epileptogenic abnormality is significant, compared to the spikes and interictal HFOs. The objectives of the study were to detect and to localize ictal HFOs by magnetoencephalography (MEG) for identifying the seizure onset zone (SOZ), evaluate the cortical excitability from preictal to ictal transition, and

establish HFO concordance rates with other modalities and postsurgical resection.

METHODS Sixty-seven patients with drug-resistant epilepsy had at least 1 spontaneous seizure each during MEG acquisition, and analysis was carried out on 20 seizures from 20 patients. Ictal MEG data were bandpass filtered (80-200 Hz) to visualize, review, and analyze the HFOs co-occurring with ictal spikes. Source montages were generated on both hemispheres, mean fast Fourier transform was computed on virtual time series for determining the preictal to ictal spectral power transition, and source reconstruction was performed with sLORETA and beamformers. The concordance rates of ictal MEG HFOs (SOZ) was estimated with 4 reference epileptogenic regions.

RESULTS In each subject, transient bursts of high-frequency oscillatory cycles, distinct from the background activity, were observed in the periictal continuum. Time-frequency analysis showed significant spectral power surge (85-160 Hz) during ictal state ($P < .05$) compared to preictal state, but there was no variation in the peak HFO frequencies ($P > .05$) for each subgroup and at each source montage. HFO source localization was consistent between algorithms ($k = 0.857 \pm 0.138$), with presumed epileptogenic zone (EZ) comparable to other modalities. In patients who underwent surgery ($n = 6$), MEG HFO SOZ was concordant with the presumed EZ and the surgical resection site (100%), and all were seizure-free during follow-up.

SIGNIFICANCE HFOs could be detected in the MEG periictal state, and its sources were accurately localized. During preictal to ictal transition, HFOs exhibited dynamic augmentation in intrinsic epileptogenicity. Spatial overlap of ictal HFO sources was consistent with EZ determinants and the surgical resection area.

Keywords: ictal HFO, ictal MEG, seizure onset zone, source localization, surgical outcome

Epilepsia (2018), Vol. 59, No. 1 (29111591)

Magnetoencephalographic Characteristics of Cortical Dysplasia in Children (2019)

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BACKGROUND AND RATIONALE Magnetoencephalography has emerged as a tool for preoperative evaluation in children. We studied magnetoencephalography characteristics in subtypes of focal cortical dysplasia and correlated the findings with postoperative seizure outcome.

METHODS Inclusion criteria were children ≤18 years who underwent magnetoencephalography during the preoperative evaluation followed by epilepsy surgery and a histopathologic diagnosis of focal cortical dysplasia between February 2008 and February 2013. Patient demographics, MRI, video electroencephalography, and magnetoencephalography data were reviewed. Postoperative seizure outcome data were categorized per International League against Epilepsy definitions.

RESULTS Of 178 magnetoencephalography studies performed in children during the study period, 33 patients met inclusion criteria. Focal cortical dysplasia type I, II, and III were found on histopathology in 52%, 39%, and 9% of patients, respectively. Thirty patients had positive magnetoencephalography dipoles, including all patients with focal cortical dysplasia type II and III and 82% of patients with focal cortical dysplasia type I. Three patients had magnetoencephalography unique spikes. Brain MRI lesions were noted preoperatively in 21 patients (64%). Twenty-three patients (77%) had surgical resection of magnetoencephalography dipoles and 11 (48%) of them achieved favorable outcome.

CONCLUSIONS Magnetoencephalography supplemented scalp electroencephalography data in spike source localization and showed unique spikes in 10% of

the focal cortical dysplasia patients. Magnetoencephalography spikes and tight magnetoencephalography clusters were found more frequently in patients with focal cortical dysplasia type II and III as compared with focal cortical dysplasia type I. Presence of an MRI lesion and complete versus incomplete resection of magnetoencephalography cluster did not result in significant difference in postoperative seizure outcome, likely reflecting selection bias of doing magnetoencephalography in only difficult-to-localize epilepsies.

Keywords: epilepsy, focal cortical dysplasia, magnetoencephalography, seizures

Pediatric neurology (2018), Vol. 78 (29074057)

Clinical yield of magnetoencephalography distributed source imaging in epilepsy: A comparison with equivalent current dipole method (2018)

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OBJECTIVE Source localization of interictal epileptic discharges (IEDs) is clinically useful in the presurgical workup of epilepsy patients. It is usually obtained by equivalent current dipole (ECD) which localizes a point source and is the only inverse solution approved by clinical guidelines. In contrast, magnetic source imaging using distributed methods (dMSI) provides maps of the location and the extent of the generators, but its yield has not been clinically validated. We systematically compared ECD versus dMSI performed using coherent Maximum Entropy on the Mean (cMEM), a method sensitive to the spatial extent of the generators.

METHODS 340 source localizations of IEDs derived from 49 focal epilepsy patients with foci well-defined through intracranial EEG, MRI lesions, and surgery were analyzed. The comparison was based on the assessment of the sublobar concordance with the focus and of the distance between the source and the focus.

RESULTS dMSI sublobar concordance was significantly higher than ECD (81% vs 69%, $P < 0.001$), especially for extratemporal lobe sources (dMSI = 84%; ECD = 67%, $P < 0.001$) and for seizure free patients (dMSI = 83%; ECD = 70%, $P < 0.001$). The median distance from the focus was 4.88 mm for ECD and 3.44 mm for dMSI ($P < 0.001$). ECD dipoles were often wrongly localized in deep brain regions.

CONCLUSIONS dMSI using cMEM exhibited better accuracy. dMSI also offered the advantage of recovering more realistic maps of the generator, which could be exploited for neuronavigation aimed at targeting invasive EEG and surgical resection. Therefore, dMSI may be preferred to ECD in clinical practice. Hum Brain Mapp 39:218-231, 2018. © 2017 Wiley Periodicals, Inc.

Keywords: MEG, dipole, distributed source, interictal epileptiform discharges, magnetic source imaging, presurgical evaluation, source localization, spike, surgery

Human brain mapping (2018), Vol. 39, No. 1 (29024165)

MEG language lateralization in partial epilepsy using dSPM of auditory event-related fields (2018)

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OBJECTIVE Methods employed to determine hemispheric language dominance using magnetoencephalography (MEG) have differed significantly across studies in the choice of language-task, the nature of the physiological response studied, recording hardware, and source modeling methods. Our goal was to determine whether an analysis based on distributed source

modeling can replicate the results of prior studies that have used dipole-modeling of event-related fields (ERFs) generated by an auditory word-recognition task to determine language dominance in patients with epilepsy.

METHODS We analyzed data from 45 adult patients with drug-resistant partial epilepsy who performed an auditory word-recognition task during MEG recording and also completed a language fMRI study as part of their evaluation for epilepsy surgery. Source imaging of auditory ERFs was performed using dynamic statistical parametric mapping (dSPM). Language laterality indices (LIs) were calculated for four regions of interest (ROIs) by counting above-threshold activations within a 300-600ms time window after stimulus onset. Language laterality (LL) classifications based on these LIs were compared to the results from fMRI.

RESULTS The most lateralized MEG responses to language stimuli were observed in a parietal region that included the angular and supramarginal gyri (AngSmg). In this region, using a half-maximal threshold, source activations were left dominant in 32 (71%) patients, right dominant in 8 (18%), and symmetric in 5 patients (11%). The best agreement between MEG and fMRI on the ternary classification of regional language dominance into left, right, or symmetric groups was also found at the AngSmg ROI (69%). This was followed by the whole-hemisphere and temporal ROIs (both 62%). The frontal ROI showed the least agreement with fMRI (51%). Gross discordances between MEG and FMRI findings were disproportionately of the type where MEG favored atypical right-hemispheric language in a patient with right-hemispheric seizure origin ($p<0.05$ at three of the four ROIs).

SIGNIFICANCE In a parietal region that includes the angular and supramarginal gyri, language laterality estimates based on dSPM of ERFs during auditory word-recognition shows a degree of MEG-fMRI concordance that is comparable to previously published estimates for MEG-Wada concordance using dipole counting methods and the same task. Our data also suggest that MEG language laterality estimates based on this task may be influenced by the laterality of epileptic networks in some patients. This has not been reported previously and deserves further study.

Keywords: Epilepsy, Language, MEG, Magnetoencephalography, fMRI, Wada

Epilepsy & behavior: E&B (2017), Vol. 73 (28662463)

Reoperation after failed resective epilepsy surgery in children (2017)

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ABSTRACT OBJECTIVE Although epilepsy surgery is an effective treatment option, at least 20%-40% of patients can continue to experience uncontrolled seizures resulting from incomplete resection of the lesion, epileptogenic zone, or secondary epileptogenesis. Reoperation could eliminate or improve seizures. Authors of this study evaluated outcomes following reoperation in a pediatric population. METHODS A retrospective single-center analysis of all patients who had undergone resective epilepsy surgery in the period from 2001 to 2013 was performed. After excluding children who had repeat hemispherotomy, there were 24 children who had undergone a second surgery and 2 children who had undergone a third surgery. All patients underwent MRI and video electroencephalography (VEEG) and 21 underwent magnetoencephalography (MEG) prior to reoperation. RESULTS The mean age at the first and second surgery was 7.66 (SD 4.11) and 10.67 (SD 4.02) years, respectively. The time between operations ranged from 0.03 to 9 years. At reoperation, 8 patients underwent extended cortical resection; 8, lobectomy; 5, lesionectomy; and 3, functional hemispherotomy. One year after reoperation, 58% of the children were completely seizure free (International League Against Epilepsy [ILAE] Class 1) and 75% had a reduction in seizures (ILAE Classes 1-4). Patients with MEG clustered dipoles were more likely to be seizure free than to have persistent seizures (71% vs 40%, $p = 0.08$). CONCLUSIONS Reoperation in children with recurrent seizures after the first epilepsy surgery could result in favorable

seizure outcomes. Those with residual lesion after the first surgery should undergo complete resection of the lesion to improve seizure outcome. In addition to MRI and VEEG, MEG should be considered as part of the reevaluation prior to reoperation.

Keywords: AED = antiepileptic drug, EEG = electroencephalography, FCD = focal cortical dysplasia, ILAE = International League Against Epilepsy, MEG = magnetoencephalography, VEEG = video-EEG, VNS = vagus nerve stimulator, magnetoencephalography, outcomes, pediatric epilepsy surgery, reoperation, repeat surgery

Journal of neurosurgery. Pediatrics (2017), Vol. 20, No. 2 (28574317)

Epileptogenic high-frequency oscillations skip the motor area in children with multilobar drug-resistant epilepsy (2017)

Iimura, Yasushi; Jones, Kevin; Hattori, Kyoko; Okazawa, Yushi; Noda, Atsuko; Hoashi, Kana; Nonoda, Yutaka; Asano, Eishi; Akiyama, Tomoyuki; Go, Cristina; Ochi, Ayako; Snead, O Carter; Donner, Elizabeth J; Rutka, James T; Drake, James M; Otsubo, Hiroshi

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OBJECTIVE Subtotal hemispherectomy involves the resection of multiple lobes in children with drug-resistant epilepsy, skipping the motor area (MA). We determined epileptogenicity using the occurrence rate (OR) of high-frequency oscillations (HFOs) and the modulation index (MI), demonstrating strength of coupling between HFO and slow wave. We hypothesized that epileptogenicity increased over the multiple lobes but skipped the MA.

METHODS We analyzed 23 children (14 subtotal hemispherectomy; 9 multilobar resections). Scalp video-EEG and magnetoencephalography were performed before surgery. We analyzed the OR(HFO) and MI(5 phases=0.5-8 Hz) on electrodes of total area, resection areas, and MA. We compared the data between good [International League Against Epilepsy (ILAE) class I-II] and poor (III-VI) seizure outcome groups.

RESULTS ILAE class Ia outcome was achieved in 18 children. Among the MI(5 phases) in the resection areas, MI(3-4 Hz) was the highest. The OR(HFO) and MI(3-4 Hz) in both total area and resection areas were significantly higher in the good seizure outcome group than in the poor outcome group. The OR(HFO) and MI(3-4 Hz) in resection areas were significantly higher than in the MA.

CONCLUSIONS Our patients with multilobar drug-resistant epilepsy showed evidence of multifocal epileptogenicity that specifically skipped the MA.

SIGNIFICANCE This is the first study demonstrating that the electrophysiological phenotype of multifocal epilepsy specifically skips the MA using OR(HFO) and MI(3-4 Hz).

Keywords: Epileptic spasms, Modulation index (MI), Motor area, Pathological high-frequency oscillations, Phase-amplitude coupling, Subtotal hemispherectomy

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2017), Vol. 128, No. 7 (28521267)

Timing and type of hemispherectomy for Rasmussen's encephalitis: Analysis of 45 patients (2018)

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OBJECTIVE To describe the surgery outcomes of RE patients in one centerto identify the indication for surgical treatment that results in the most favorable outcome.

METHOD Forty-five RE patients from a single center were retrospectively reviewed. Preoperative evaluations included assessments of clinical manifestations, cognitive status, a physical examination, MRI, positron emission tomography (PET), electroencephalography (EEG), and magnetoencephalography (MEG). The surgical outcomes included seizure outcome, neurological function, EEG, a cognitive evaluation, and antiepileptic drug withdrawal.

RESULTS A total of 45 children (29 male) with RE were included in this study. The mean follow-up period from the first operation was 31.7months (range 6-96). The patients who underwent anatomical hemispherectomy or hemisphere disconnection had better seizure outcomes without greater perioperative complications compared with the patients who underwent functional hemispherectomy. Reoperative hemispherectomy was a safe and effective treatment for patients with postoperative epilepsy recurrence. After the last surgery, 34 patients (74.4%) were evaluated as Engel class I. Most of the patients had favorable neurological outcomes. Analysis revealed that the patientswith IQs greater 70 who underwent operations were more likely to suffer from IQ declines but were also more likely to have higher IQs in the future.

SIGNIFICANCE Compared with functional hemispherectomy and hemisphere disconnection, anatomical hemispherectomy elicited better seizure outcomes with an acceptable level of complications. Early stage operations might lead to better cognitive status, but they are associated with a high risk of IQ decline.

Keywords: Functional outcome, Hemispherectomy, Rasmussen's encephalitis (or Rasmussen encephalitis, RE), Seizure outcome

Epilepsy research (2017), Vol. 132 (28399506)

Navigation-assisted trans-inferotemporal cortex selective amygdalohippocampectomy for mesial temporal lobe epilepsy; preserving the temporal stem (2017)

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OBJECTIVE Selective amygdalohippocampectomy (SAH) can be used to obtain satisfactory seizure control in patients with mesial temporal lobe epilepsy (MTLE). Several SAH procedures have been reported to achieve satisfactory outcomes for seizure control, but none yield fully satisfactory outcomes for memory function. We hypothesized that preserving the temporal stem might play an important role. To preserve the temporal stem, we developed a minimally invasive surgical procedure, 'neuronavigation-assisted trans-inferotemporal cortex SAH' (TITC-SAH).

METHODS TITC-SAH was performed in 23 patients with MTLE (MTLE on the language-non-dominant hemisphere, n = 11). The inferior horn of the lateral ventricle was approached via the inferior or middle temporal gyrus along the inferior temporal sulcus under neuronavigation guidance. The hippocampus was dissected in a subpial manner and resected en bloc together with the parahippocampal gyrus. Seizure control at one year and memory function at 6 months postoperatively were evaluated.

RESULTS One year after TITC-SAH, 20 of the 23 patients were seizure-free (ILAE class 1), 2 were class 2, and 1 was class 3. Verbal memory improved significantly in 13 patients with a diagnosis of hippocampal sclerosis, for whom WMS-R scores were available both pre- and

post-operatively. Improvements were seen regardless of whether the SAH was on the language-dominant or non-dominant hemisphere. No major complication was observed.

CONCLUSION Navigation-assisted TITC-SAH performed for MTLE offers a simple, minimally invasive procedure that appears to yield excellent outcomes in terms of seizure control and preservation of memory function, because this procedure does not damage the temporal stem. TITC-SAH should be one of the feasible surgical procedures for MTLE.

ABBREVIATIONS SAH: Amygdalohippocampectomy; MTLE: Mesial temporal lobe epilepsy (MTLE); TITC-SAH: Ttrans-inferotemporal cortex SAH; ILAE: International League Against Epilepsy (ILAE); MRI: Magnetic resonance imaging; EEG: Electroencephalography (EEG); FDG-PET: [8]F-fluorodeoxyglucose (FDG)-positron emission tomography; ECoG: Electrocorticography; MEG: Magnetoencephalography; IMZ-SPECT: N-isopropyl-p([123]I)-iodoamphetamine single photon emission computed tomography; WMS-R: Wechsler Memory Scale-Revised.

Keywords: Mesial temporal lobe epilepsy, memory outcomes, minimally invasive, navigation-assisted trans-inferotemporal cortex-selective amygdalohippocampectomy, temporal stem

Neurological research (2017), Vol. 39, No. 3 (28067149)

Electrophysiological resting-state biomarker for diagnosing mesial temporal lobe epilepsy with hippocampal sclerosis (2018)

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ABSTRACT The main aim of the present study was to evaluate whether resting-state functional connectivity of magnetoencephalography (MEG) signals can differentiate patients with mesial temporal lobe epilepsy (MTLE) from healthy controls (HC) and can differentiate between right and left MTLE as a diagnostic biomarker. To this end, a support vector machine (SVM) method among various machine learning algorithms was employed. We compared resting-state functional networks between 46 MTLE (right MTLE=23; left MTLE=23) patients with histologically proven HS who were free of seizure after surgery, and 46 HC. The optimal SVM group classifier distinguished MTLE patients with a mean accuracy of 95.1% (sensitivity=95.8%; specificity=94.3%). Increased connectivity including the right posterior cingulate gyrus and decreased connectivity including at least one sensory-related resting-state network were key features reflecting the differences between MTLE patients and HC. The optimal SVM model distinguished between right and left MTLE patients with a mean accuracy of 76.2% (sensitivity=76.0%; specificity=76.5%). We showed the potential of electrophysiological resting-state functional connectivity, which reflects brain network reorganization in MTLE patients, as a possible diagnostic biomarker to differentiate MTLE patients from HC and differentiate between right and left MTLE patients.

Keywords: Mesial temporal lobe epilepsy, Resting-state magnetoencephalography, Support vector machine

Epilepsy research (2017), Vol. 129 (28043064)

Source localization of epileptiform discharges in juvenile myoclonic epilepsy (JME) using magnetoencephalography (MEG) (2018)

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OBJECTIVE The purpose of this study is to localize the sources of epileptiform discharges (EDs), in juvenile myoclonic epilepsy (JME) using Magnetoencephalography (MEG), at three different time instances and analyze the propagation of EDs, from onset to offset, for inferring the cortical and subcortical region of involvement.

METHODS Twenty patients (age 23.5±6.3years old) with JME were recruited in this prospective study. MEG source analysis was performed on the independently collected EDs of each patient. The distributed source model was employed for source localization using low resolution electromagnetic brain tomography (LORETA). In each EDs, the onset (leading edge of the spike from baseline), peak and offset (trailing edge of the spike), with time window of 8ms, were subjected for source localization in order to study the propagation of the EDs. The obtained source location coordinates, from each individual MRI, were transformed in Talairach space and the distribution of region of source involvement was analysed.

RESULTS The frequency pattern of lobar distribution at onset, peak and offset respectively suggest that discharges most commonly localized at onset from sublobar region, at peak from frontal lobe and at offset from the sublobar region. It was observed that the maximum involvement of sources from the sublobar, limbic and frontal lobes at different time instances. It indicates that the restricted cortical-subcortical involvement during the generation and propagation of EDs in JME.

SIGNIFICANCE This MEG study supported the cortical-subcortical region of involvement and provided further insights in our understanding the network involvement in generation and propagation of EDs in JME.

Keywords: Epileptiform discharges, IGE, JME, MEG, Source analysis

Epilepsy research (2017), Vol. 129 (27918962)

Identifying the epileptogenic zone in interictal resting-state MEG source-space networks (2017)

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OBJECTIVE In one third of patients, seizures remain after epilepsy surgery, meaning that improved preoperative evaluation methods are needed to identify the epileptogenic zone. A potential framework for such a method is network theory, as it can be applied to non-invasive recordings, even in the absence of epileptiform activity. Our aim was to identify the epileptogenic zone on the basis of hub status of local brain areas in interictal magnetoencephalography (MEG) networks.

METHODS Preoperative eyes-closed resting-state MEG recordings were retrospectively analyzed in 22 patients with refractory epilepsy, of whom 14 were seizure-free 1 year after surgery. Beamformer-based time series were reconstructed for 90 cortical and subcortical automated anatomic labeling (AAL) regions of interest (ROIs). Broadband functional connectivity was estimated using the phase lag index in artifact-free epochs without interictal epileptiform abnormalities. A minimum spanning tree was generated to represent the network, and the hub status of each ROI was calculated using betweenness centrality, which indicates the centrality of a node in a network. The correspondence of resection cavity to hub values was evaluated on four levels: resection cavity, lobar, hemisphere, and temporal versus extratemporal areas.

RESULTS Hubs were localized within the resection cavity in 8 of 14 seizure-free patients and in zero of 8 patients who were not seizure-free (57% sensitivity, 100% specificity, 73% accuracy). Hubs were localized in the lobe of resection in 9 of 14 seizure-free patients and in zero of 8 patients who were not seizure-free (64% sensitivity, 100% specificity, 77% accuracy). For the other two levels, the true negatives are unknown; hence, only sensitivity could be determined: hubs coincided with both the resection hemisphere and the resection location (temporal versus extratemporal) in 11 of 14 seizure-free patients (79% sensitivity).

SIGNIFICANCE Identifying hubs noninvasively before surgery is a valuable approach with the potential of indicating the epileptogenic zone in patients without interictal abnormalities.

Keywords: Beamformer-based virtual electrodes, Betweenness centrality, Epilepsy, Functional network, Hub, Neurosurgery

Epilepsia (2017), Vol. 58, No. 1 (27888520)

Language

MEG language lateralization in partial epilepsy using dSPM of auditory event-related fields (2018)

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OBJECTIVE Methods employed to determine hemispheric language dominance using magnetoencephalography (MEG) have differed significantly across studies in the choice of language-task, the nature of the physiological response studied, recording hardware, and source modeling methods. Our goal was to determine whether an analysis based on distributed source modeling can replicate the results of prior studies that have used dipole-modeling of event-related fields (ERFs) generated by an auditory word-recognition task to determine language dominance in patients with epilepsy.

METHODS We analyzed data from 45 adult patients with drug-resistant partial epilepsy who performed an auditory word-recognition task during MEG recording and also completed a language fMRI study as part of their evaluation for epilepsy surgery. Source imaging of auditory ERFs was performed using dynamic statistical parametric mapping (dSPM). Language laterality indices (LIs) were calculated for four regions of interest (ROIs) by counting above-threshold activations within a 300-600ms time window after stimulus onset. Language laterality (LL) classifications based on these LIs were compared to the results from fMRI.

RESULTS The most lateralized MEG responses to language stimuli were observed in a parietal region that included the angular and supramarginal gyri (AngSmg). In this region, using a half-maximal threshold, source activations were left dominant in 32 (71%) patients, right dominant in 8 (18%), and symmetric in 5 patients (11%). The best agreement between MEG and fMRI on the ternary classification of regional language dominance into left, right, or symmetric groups was also found at the AngSmg ROI (69%). This was followed by the whole-hemisphere and temporal ROIs (both 62%). The frontal ROI showed the least agreement with fMRI (51%). Gross discordances between MEG and FMRI findings were disproportionately of the type where MEG favored atypical right-hemispheric language in a patient with right-hemispheric seizure origin ($p<0.05$ at three of the four ROIs).

SIGNIFICANCE In a parietal region that includes the angular and supramarginal gyri, language laterality estimates based on dSPM of ERFs during auditory word-recognition shows a degree of MEG-fMRI concordance that is comparable to previously published estimates for MEG-Wada concordance using dipole counting methods and the same task. Our data also suggest that MEG language laterality estimates based on this task may be influenced by the laterality of epileptic networks in some patients. This has not been reported previously and deserves further study.

Keywords: Epilepsy, Language, MEG, Magnetoencephalography, fMRI, Wada

Epilepsy & behavior: E&B (2017), Vol. 73 (28662463)

Migraine

Abnormal functional connectivity under somatosensory stimulation in migraine: a multi-frequency magnetoencephalography study (2019)

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BACKGROUND Although altered neural networks have been demonstrated in recent MEG (magnetoencephalography) research in migraine patients during resting state, it is unknown whether this alteration can be detected in task-related networks. The present study aimed to investigate the abnormalities of the frequency-specific somatosensory-related network in migraine patients by using MEG.

METHODS Twenty-two migraineurs in the interictal phase and twenty-two sex- and age-matched healthy volunteers were studied using a whole-head magnetoencephalography (MEG) system. Electrical stimuli were delivered alternately to the median nerve on the right wrists of all subjects. MEG data were analyzed in a frequency range of 1-1000 Hz in multiple bands.

RESULTS The brain network patterns revealed that the patients with migraine exhibited remarkably increased functional connectivity in the high-frequency (250-1000 Hz) band between the sensory cortex and the frontal lobe. The results of quantitative analysis of graph theory showed that the patients had (1) an increased degree of connectivity in the theta (4-8 Hz), beta (13-30 Hz) and gamma (30-80 Hz) bands; (2) an increased connectivity strength in the beta (13-30 Hz) and gamma (30-80 Hz) bands; (3) an increased path length in the beta (13-30 Hz), gamma (30-80 Hz) and ripple (80-250 Hz) bands; and (4) an increased clustering coefficient in the theta (4-8 Hz), beta (13-30 Hz) and gamma (30-80 Hz) bands.

CONCLUSIONS The results indicate that migraine is associated with aberrant connections from the somatosensory cortex to the frontal lobe. The frequency-specific increases in connectivity in terms of strength, path length and clustering coefficients support the notion that migraineurs have elevated cortical networks. This alteration in functional connectivity may be involved in somatosensory processing in migraine patients and may contribute to understanding migraine pathophysiology and to providing convincing evidence for a spatially targeted migraine therapy.

Keywords: Functional connectivity, Magnetoencephalography, Migraine, Multi-frequency, Somatosensory

The journal of headache and pain (2019), Vol. 20, No. 1 (30626318)

Comparison of somatosensory cortex excitability between migraine and "strict-criteria" tension-type headache: a magnetoencephalographic study (2019)

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ABSTRACT Tension-type headache (TTH) and migraine are both common types of headaches. Despite distinct

symptoms, TTH and migraine are highly comorbid and exhibit many clinical similarities. This study enrolled consecutive patients with TTH and age- and sex-matched patients with migraine and healthy controls to investigate whether TTH and migraine are similar in brain excitability change assessed by magnetoencephalography. Patients with TTH were excluded if they reported any headache features or associated symptoms of migraine. In response to paired-pulse electrical stimulations, the gating responses obtained from the contralateral primary somatosensory cortex differed between groups. The first response, which reflected the preactivation excitability, was smaller in the migraine group (29.54 ± 2.31 pAm) compared with the TTH group (79.76 ± 8.36, P < 0.001) and controls (59.95 ± 4.26, P = 0.006). The gating ratio (ie, the ratio of the second vs first response strength) was 0.76 ± 0.03 in controls, 0.88 ± 0.03 in the migraine group, 0.93 ± 0.03 in the TTH group, with a significant increase in TTH (P = 0.003 vs controls) suggesting central disinhibition. The area under the receiver operating characteristic curve of the first response strength in differentiating between TTH and migraine was 0.85 ± 0.44, indicating excellent discrimination. In conclusion, TTH and migraine are different clinical entities in view of somatosensory cortex excitability. The preactivation excitability assessed through somatosensory gating is a potential marker for differentiating between TTH and migraine.

Pain (2018), Vol. 159, No. 4 (29319611)

Somatosensory gating is altered and associated with migraine chronification: A magnetoencephalographic study (2019)

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ABSTRACT Background Brain excitability is changed in migraine but not fully characterized yet. This study explored if somatosensory gating is altered in migraine and linked to migraine chronification. Methods Paired electrical stimuli were delivered to the left index fingers of 21 patients with migraine without aura (MO), 22 patients with chronic migraine (CM), and 36 controls. The first and second responses to the paired stimuli were obtained from the contralateral primary (cSI), contralateral secondary (cSII) and ipsilateral secondary (iSII) somatosensory cortices to compute the gating ratios (second vs. first response strengths). Results The first and second cSI responses and gating ratios differed in all groups ($p < 0.05$); the responses were typically smaller in the MO and CM groups. The cSI gating ratio increased as a continuum across controls (0.73 ± 0.04, $p < 0.001$), MO (0.83 ± 0.04) to CM (0.97 ± 0.06) and was higher in CM vs. controls ($p < 0.001$). When MO and CM were combined, cSI gating ratio was associated with headache frequency ($r = 0.418$, $p = 0.005$). Paired responses and gating ratios of cSII and iSII did not differ among the groups. Conclusions Somatosensory gating is altered in migraine and associated with headache chronification. Further studies must clarify if this abnormal sensory modulation is a true gating deficit independent of low preexcitation level.

Keywords: Sensory gating, chronic migraine, magnetoencephalography (MEG), migraine, primary somatosensory cortex

Cephalalgia: an international journal of headache (2018), Vol. 38, No. 4 (28540738)

Multiple Sclerosis

Altered transient brain dynamics in multiple sclerosis: Treatment or pathology? (2020)

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ABSTRACT Multiple sclerosis (MS) is a demyelinating, neuroinflammatory, and -degenerative disease that affects the brain's neurophysiological functioning through brain atrophy, a reduced conduction velocity and decreased connectivity. Currently, little is known on how MS affects the fast temporal dynamics of activation and deactivation of the different large-scale, ongoing brain networks. In this study, we investigated whether these temporal dynamics are affected in MS patients and whether these changes are induced by the pathology or by the use of benzodiazepines (BZDs), an important symptomatic treatment that aims at reducing insomnia, spasticity and anxiety and reinforces the inhibitory effect of GABA. To this aim, we employed a novel method capable of detecting these fast dynamics in 90 MS patients and 46 healthy controls. We demonstrated a less dynamic frontal default mode network in male MS patients and a reduced activation of the same network in female MS patients, regardless of BZD usage. Additionally, BZDs strongly altered the brain's dynamics by increasing the time spent in the deactivating sensorimotor network and the activating occipital network. Furthermore, BZDs induced a decreased power in the theta band and an increased power in the beta band. The latter was strongly expressed in those states without activation of the sensorimotor network. In summary, we demonstrate gender-dependent changes to the brain dynamics in the frontal DMN and strong effects from BZDs. This study is the first to characterise the effect of multiple sclerosis and BZDs in vivo in a spatially, temporally and spectrally defined way.

Keywords: benzodiazepines, hidden Markov model, multiple sclerosis, transient brain dynamics

Human brain mapping (2019), Vol. 40, No. 16 (31361073)

Resting-state MEG measurement of functional activation as a biomarker for cognitive decline in MS (2020)

Schoonhoven, Deborah N; Fraschini, Matteo; Tewarie, Prejaas; Uitdehaag, Bernard Mj; Eijlers, Anand Jc; Geurts, Jeroen Jg; Hillebrand, Arjan; Schoonheim, Menno M; Stam, Cornelis J; Strijbis, Eva Mm

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BACKGROUND Neurophysiological measures of brain function, such as magnetoencephalography (MEG), are widely used in clinical neurology and have strong relations with cognitive impairment and dementia but are still underdeveloped in multiple sclerosis (MS).

OBJECTIVES To demonstrate the value of clinically applicable MEG-measures in evaluating cognitive impairment in MS.

METHODS In eyes-closed resting-state, MEG data of 83 MS patients and 34 healthy controls (HCs) peak frequencies and relative power of six canonical frequency bands for 78 cortical and 10 deep gray matter (DGM) areas were calculated. Linear regression models, correcting for age, gender, and education, assessed the relation between cognitive performance and MEG biomarkers.

RESULTS Increased alpha1 and theta power was strongly associated with impaired cognition in patients, which differed between cognitively impaired (CI) patients and HCs in bilateral parietotemporal cortices. CI patients had a lower peak frequency than HCs. Oscillatory slowing was also widespread in the DGM, most pronounced in the thalamus.

CONCLUSION There is a clinically relevant slowing of neuronal activity in MS patients in parietotemporal cortical areas and the thalamus, strongly related to cognitive impairment. These measures hold promise for the application of resting-state MEG as a biomarker for cognitive disturbances in MS in a clinical setting.

Keywords: Multiple sclerosis, cognition, magnetoencephalography, oscillatory activity, power

Multiple sclerosis (Houndmills, Basingstoke, England) (2019), Vol. 25, No. 14 (30465461)

Neuropathic pain and pain interference are linked to alpha-band slowing and reduced beta-band magnetoencephalography activity within the dynamic pain connectome in patients with multiple sclerosis (2019)

Kim, Junseok A; Bosma, Rachael L; Hemington, Kasey S; Rogachov, Anton; Osborne, Natalie R; Cheng, Joshua C; Oh, Jiwon; Crawley, Adrian P; Dunkley, Ben T; Davis, Karen D

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ABSTRACT Chronic pain is a common occurrence in multiple sclerosis (MS) that severely affects quality of life, but the underlying brain mechanisms related to these symptoms are unknown. Previous electroencephalography studies have demonstrated a role of alpha-band and beta-band power in pain processing. However, how and where these brain signals change in MS-related chronic pain is unknown. Here, we used resting state magnetoencephalography to examine regional spectral power in the dynamic pain connectome-including areas of the ascending nociceptive pathway, default mode network (DMN), and the salience network (SN)-in patients with chronic MS pain and in healthy controls. Each patient was assessed for pain, neuropathic pain (NP), and pain interference with activities of daily living. We found that patients with MS exhibited an increase of alpha-band power and a decrease of beta-band power, most prominently in the thalamus and the posterior insula of the ascending nociceptive pathway and in the right temporoparietal junction of the SN. In addition, patients with mixed-NP exhibited slowing of alpha peak power within the thalamus and the posterior insula, and in the posterior cingulate cortex of the DMN. Finally, pain interference scores in patients with mixed-NP were strongly corre-

lated with alpha and beta peak power in the thalamus and posterior insula. These novel findings reveal brain mechanisms of MS-related pain in the ascending nociceptive pathway, SN, and DMN, and that these spectral abnormalities reflect the impact of pain on quality of life measures.

Pain (2019), Vol. 160, No. 1 (30188456)

Abnormal task driven neural oscillations in multiple sclerosis: A visuomotor MEG study (2018)

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ABSTRACT Multiple sclerosis (MS) is a debilitating disease commonly attributed to degradation of white matter myelin. Symptoms include fatigue, as well as problems associated with vision and movement. Although areas of demyelination in white matter are observed routinely in patients undergoing MRI scans, such measures are often a poor predictor of disease severity. For this reason, it is instructive to measure associated changes in brain function. Widespread white-matter demyelination may lead to delays of propagation of neuronal activity, and with its excellent temporal resolution, magnetoencephalography can be used to probe such delays in controlled conditions (e.g., during a task). In healthy subjects, responses to visuomotor tasks are well documented: in motor cortex, movement elicits a localised decrease in the power of beta band oscillations (event-related beta desynchronisation) followed by an increase above baseline on movement cessation (post-movement beta rebound (PMBR)). In visual cortex, visual stimulation generates increased gamma oscillations. In this study, we use a visuomotor paradigm to measure these responses in MS patients and compare them to age- and gender-matched healthy controls. We show a significant increase in the time-to-peak of the PMBR in patients which correlates significantly with the symbol digit modalities test: a measure of information processing speed. A significant decrease in the amplitude of visual gamma oscillations in patients is also seen. These findings highlight the potential value of electrophysiological imaging in generating a new understanding of visual disturbances and abnormal motor control in MS patients. Hum Brain Mapp 38:2441-2453, 2017. © 2017 Wiley Periodicals, Inc.

Keywords: MEG, multiple sclerosis, neuronal oscillations, post-movement beta rebound, visual gamma, visuomotor abnormalities

Human brain mapping (2017), Vol. 38, No. 5 (28240392)

Pain

Individual pain sensitivity is associated with resting-state cortical activities in healthy individuals but not in patients with migraine: a magnetoencephalography study (2020)

Hsiao, Fu-Jung; Chen, Wei-Ta; Liu, Hung-Yu; Wang, Yen-Feng; Chen, Shih-Pin; Lai, Kuan-Lin; Pan, Li-Ling Hope; Wang, Shuu-Jiun

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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)

Neuropathic pain and pain interference are linked to alpha-band slowing and reduced beta-band magnetoencephalography activity within the dynamic pain connectome in patients with multiple sclerosis (2019)

Kim, Junseok A; Bosma, Rachael L; Hemington, Kasey S; Rogachov, Anton; Osborne, Natalie R; Cheng, Joshua C;

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ABSTRACT Chronic pain is a common occurrence in multiple sclerosis (MS) that severely affects quality of life, but the underlying brain mechanisms related to these symptoms are unknown. Previous electroencephalography studies have demonstrated a role of alpha-band and beta-band power in pain processing. However, how and where these brain signals change in MS-related chronic pain is unknown. Here, we used resting state magnetoencephalography to examine regional spectral power in the dynamic pain connectome-including areas of the ascending nociceptive pathway, default mode network (DMN), and the salience network (SN)-in patients with chronic MS pain and in healthy controls. Each patient was assessed for pain, neuropathic pain (NP), and pain interference with activities of daily living. We found that patients with MS exhibited an increase of alpha-band power and a decrease of beta-band power, most prominently in the thalamus and the posterior insula of the ascending nociceptive pathway and in the right temporoparietal junction of the SN. In addition, patients with mixed-NP exhibited slowing of alpha peak power within the thalamus and the posterior insula, and in the posterior cingulate cortex of the DMN. Finally, pain interference scores in patients with mixed-NP were strongly correlated with alpha and beta peak power in the thalamus and posterior insula. These novel findings reveal brain mechanisms of MS-related pain in the ascending nociceptive pathway, SN, and DMN, and that these spectral abnormalities reflect the impact of pain on quality of life measures.

Pain (2019), Vol. 160, No. 1 (30188456)

Encoding of menstrual pain experience with theta oscillations in women with primary dysmenorrhea (2019)

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ABSTRACT Theta oscillation (4-7 Hz) is well documented for its association with neural processes of memory. Pronounced increase of theta activity is commonly observed in patients with chronic neurogenic pain. However, its association with encoding of pain experience in patients with chronic pain is still unclear. The goal of the present study is to investigate the theta encoding of sensory and emotional information of long-term menstrual pain in women with primary dysmenorrhea (PDM). Forty-six young women with PDM and 46 age-matched control subjects underwent resting-state magnetoencephalography study during menstrual and periovulatory phases. Our results revealed increased theta activity in brain regions of pain processing in women with PDM, including the right parahippocampal gyrus, right posterior insula, and left anterior/middle cingulate gyrus during the menstrual phase and the left anterior insula and the left middle/inferior temporal gyrus during the periovulatory phase. The correlations between theta activity and the psychological measures pertaining to pain experience (depression, state anxiety, and pain rating index) implicate the role of theta oscillations in emotional and sensory processing of pain. The present study provides evidence for the role of theta oscillations in encoding the immediate and sustained effects of pain experience in young women with PDM.

Scientific reports (2017), Vol. 7, No. 1 (29167518)

Expectation violation and attention to pain jointly modulate neural gain in somatosensory cortex (2018)

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ABSTRACT The neural processing and experience of pain are influenced by both expectations and attention. For example, the amplitude of event-related pain responses is enhanced by both novel and unexpected pain, and by moving the focus of attention towards a painful stimulus. Under predictive coding, this congruence can be explained by appeal to a precision-weighting mechanism, which mediates bottom-up and top-down attentional processes by modulating the influence of feedforward and feedback signals throughout the cortical hierarchy. The influence of expectation and attention on pain processing can be mapped onto changes in effective connectivity between or within specific neuronal populations, using a canonical microcircuit (CMC) model of hierarchical processing. We thus implemented a CMC within dynamic causal modelling for magnetoencephalography in human subjects, to investigate how expectation violation and attention to pain modulate intrinsic (within-source) and extrinsic (between-source) connectivity in the somatosensory hierarchy. This enabled us to establish whether both expectancy and attentional processes are mediated by a similar precision-encoding mechanism within a network of somatosensory, frontal and parietal sources. We found that both unexpected and attended pain modulated the gain of superficial pyramidal cells in primary and secondary somatosensory cortex. This modulation occurred in the context of increased lateralized recurrent connectivity between somatosensory and fronto-parietal sources, driven by unexpected painful occurrences. Finally, the strength of effective connectivity parameters in S1, S2 and IFG predicted individual differences in subjective pain modulation ratings. Our findings suggest that neuromodulatory gain control in the somatosensory hierarchy underlies the influence of both expectation violation and attention on cortical processing and pain perception.

NeuroImage (2017), Vol. 153 (28341164)

Maternal Depression Across the First Years of Life Impacts the Neural Basis of Empathy in Preadolescence (2017)

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OBJECTIVE Exposure to maternal depression across the first years of life markedly increases children's susceptibility to psychopathology, yet no study has tested its effects on the maturation of children's social brain.

METHOD Using a birth cohort of mothers with no contextual risk (N = 1,983), families were followed at 7 time points from birth to 11 years and repeatedly assessed for maternal depression across the first 6 years to form 2 cohorts: mothers continuously depressed from birth to 6 years and controls without depression. At 11 years of age, children's (n = 72; depressed, n = 27; nondepressed, n = 45) brain response to others' pain was measured by magnetoencephalography.

RESULTS Preadolescents displayed a unique oscillatory pattern with higher alpha power to pain versus no pain

expressing as alpha rebound, not alpha suppression, at a late time window (1,100-1,300 ms post-stimulus) in the supplementary motor area. This suggests that top-down processing in areas of the pain matrix can underpin the maturation of vicarious empathy. Children of mothers with depression showed enhanced alpha rebound to pain in the right posterior superior temporal gyrus, which was unrelated to emotion detection abilities, pointing to decreased late processing of others' overwhelming experiences in socio-cognitive areas. Alpha power in the posterior superior temporal gyrus was predicted by higher maternal intrusiveness and lower synchrony across early childhood.

CONCLUSION These findings, from the first study to examine maternal depression and early caregiving as long-term predictors of children's neural empathic response, pinpoint a decrease in top-down socio-cognitive mechanisms as potential pathways for the cross-generational transfer of vulnerability from mothers with depression to their offspring and highlight the need for early interventions focused on enhancing maternal attunement.

Keywords: alpha oscillations, empathy, magnetoencephalography, maternal depression, mother–child interaction

Journal of the American Academy of Child and Adolescent Psychiatry (2017), Vol. 56, No. 1 (27993224)

Decoding the perception of endogenous pain from resting-state MEG (2018)

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ABSTRACT Decoding the neural representations of pain is essential to obtaining an objective assessment as well as an understanding of its underlying mechanisms. The complexities involved in the subjective experience of pain make it difficult to obtain a quantitative assessment from the induced spatiotemporal patterns of brain activity of high dimensionality. Most previous studies have investigated the perception of pain by analyzing the amplitude or spatial patterns in the response of the brain to external stimulation. This study investigated the decoding of endogenous pain perceptions according to resting-state magnetoencephalographic (MEG) recordings. In our experiments, we applied a beamforming method to calculate the brain activity for every brain region and examined temporal and spectral features of brain activity for predicting the intensity of perceived pain in patients with primary dysmenorrhea undergoing menstrual pain. Our results show that the asymmetric index of sample entropy in the precuneus and the sample entropy in the left posterior cingulate gyrus were the most informative characteristics associated with the perception of menstrual pain. The correlation coefficient (ρ=0.64, $p<0.001$) between the predicted and self-reported pain scores demonstrated the high prediction accuracy. In addition to the estimated brain activity, we were able to predict accurate pain scores directly from MEG channel signals (ρ=0.65, $p<0.001$). These findings suggest the possibility of using the proposed model based on resting-state MEG to predict the perceived intensity of endogenous pain.

Keywords: Decoding, Endogenous pain, Pain perception, Resting-state MEG

NeuroImage (2017), Vol. 144, No. Pt A (27746387)

Parkinson's Disease

Pre-stimulus beta power modulation during motor sequence learning is reduced in 'Parkinson's disease (2020)

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ABSTRACT Beta oscillations within motor-cortical areas have been linked to sensorimotor function. In line with this, pathologically altered beta activity in cortico-basal ganglia pathways has been suggested to contribute to the pathophysiology of Parkinson's disease (PD), a neurodegenerative disorder primarily characterized by motor impairment. Although its precise function is still discussed, beta activity might subserve an anticipatory role in preparation of future actions. By reanalyzing previously published data, we aimed at investigating the role of pre-stimulus motor-cortical beta power modulation in motor sequence learning and its alteration in PD. 20 PD patients and 20 healthy controls (HC) performed a serial reaction time task (SRTT) in which reaction time gain presumably reflects the ability to anticipate subsequent sequence items. Randomly varying patterns served as control trials. Neuromagnetic activity was recorded using magnetoencephalography (MEG) and data was reanalyzed with respect to task stimuli onset. Assuming that pre-stimulus beta power modulation is functionally related to motor sequence learning, reaction time gain due to training on the SRTT should vary depending on the amount of beta power suppression prior to stimulus onset. We hypothesized to find less pre-stimulus beta power suppression in PD patients as compared to HC associated with reduced motor sequence learning in patients. Behavioral analyses revealed that PD patients exhibited smaller reaction time gain in sequence relative to random control trials than HC indicating reduced learning in PD. This finding was indeed paralleled by reduced pre-stimulus beta power suppression in PD patients. Further strengthening its functional relevance, the amount of pre-stimulus beta power suppression during sequence training significantly predicted subsequent reaction time advantage in sequence relative to random trials in patients. In conclusion, the present data provide first evidence for the contribution of pre-stimulus motor-cortical beta power suppression to motor sequence learning and support the hypothesis that beta oscillations may subserve an anticipatory, predictive function, possibly compromised in PD.

Keywords: Anticipatory motor control, Beta oscillations, Magnetoencephalography (MEG), Parkinson's disease (PD), SRTT

NeuroImage. Clinical (2019), Vol. 24 (31715558)

Auditory entrainment of motor responses in older adults with and without Parkinson's disease: An MEG study (2020)

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ABSTRACT Medical therapies applied to Parkinson's disease (PD) have advanced tremendously since the 1960's based on advances in our understanding of the underlying neurophysiology. Behavioral therapies, such as rhythmic auditory stimulation (RAS), have been developed more recently and demonstrated efficacy. However, the neural mechanisms of RAS are only vaguely understood. In this study, we examined the neurophysiology of RAS using magnetoencephalography (MEG) in a sample of older adults with (21 people) and without PD (23 participants). All participants underwent high-density MEG during a beat-based cued tapping task with rhythmic and non-rhythmic patterns, and the resulting data were analyzed using a Bayesian image reconstruction method. Complex wavelet based time-frequency decomposition was used to compute inter-trial phase locking factor (PLF) to auditory stimuli for left and right signal space projection vectors. Tapping with a rhythm compared to a non-rhythmic sequence resulted in differential brain activity in each group: (i) a greater activation of temporal, motor and parietal areas was found in healthy adults; (ii) a greater reliance on parietal and frontal gyri was found in PD participants. During rhythmic tapping, older adults without PD had significantly stronger neural activity in bilateral frontal, supplementary and primary motor areas compared to those with PD. Conversely, older adults with PD exhibited significantly stronger activity in the bilateral parietal regions, as well as the rolandic operculum and bilateral supramarginal gyri, relative to their healthy peers. These data suggest that RAS mobilizes diverse oscillatory networks; Healthy controls may shift to frontal areas mobilization whereas PD patients rely on parietal areas to a greater extent, which may reflect frontal network dysfunction with compensation in PD, and could serve as specific regions of interest for further RAS studies.

Keywords: Auditory-motor, Networks, Neurophysiology, Rhythm, Tapping

Neuroscience letters (2019), Vol. 708 (31226362)

Aberrant resting-state oscillatory brain activity in Parkinson's disease patients with visual hallucinations: An MEG source-space study (2020)

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ABSTRACT To gain insight into possible underlying mechanism(s) of visual hallucinations (VH) in Parkinson's disease (PD), we explored changes in local oscillatory activity in different frequency bands with source-space magnetoencephalography (MEG). Eyes-closed resting-state MEG recordings were obtained from 20 PD patients with hallucinations (Hall+) and 20 PD patients without hallucinations (Hall-), matched for age, gender and disease severity. The Hall+ group was subdivided into 10 patients with VH only (unimodal Hall+) and 10 patients with multimodal hallucinations (multimodal Hall+). Subsequently, neuronal activity at source-level was reconstructed using an atlas-based beamforming approach resulting in source-space time series for 78 cortical and 12 subcortical regions of interest in the automated anatomical labeling (AAL) atlas. Peak frequency (PF) and relative power in six frequency bands (delta, theta, alpha1, alpha2, beta and gamma) were compared between Hall+ and Hall-, unimodal Hall+ and Hall-, multimodal Hall+ and Hall-, and unimodal Hall+ and multimodal Hall+ patients. PF and relative power per frequency band did not differ between Hall+ and Hall-, and multimodal Hall+ and Hall- patients.

Compared to the Hall- group, unimodal Hall+ patients showed significantly higher relative power in the theta band ($p = 0.005$), and significantly lower relative power in the beta ($p = 0.029$) and gamma ($p = 0.007$) band, and lower PF ($p = 0.011$). Compared to the unimodal Hall+, multimodal Hall+ showed significantly higher PF ($p = 0.007$). In conclusion, a subset of PD patients with only VH showed slowing of MEG-based resting-state brain activity with an increase in theta activity, and a concomitant decrease in beta and gamma activity, which could indicate central cholinergic dysfunction as underlying mechanism of VH in PD. This signature was absent in PD patients with multimodal hallucinations.

Keywords: Cholinergic dysfunction, MEG, Multimodal hallucinations, Parkinson's disease, Visual hallucinations

NeuroImage. Clinical (2019), Vol. 22 (30897434)

The significance of brain oscillations in motor sequence learning: Insights from Parkinson's disease (2019)

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ABSTRACT Motor sequence learning plays a pivotal role in various everyday activities. Motor-cortical beta oscillations have been suggested to be involved in this type of learning. In Parkinson's disease (PD), oscillatory activity within cortico-basal-ganglia circuits is altered. Pathologically increased beta oscillations have received particular attention as they may be associated with motor symptoms such as akinesia. In the present magnetoencephalography (MEG) study, we investigated PD patients and healthy controls (HC) during implicit motor sequence learning with the aim to shed light on the relation between changes of cortical brain oscillations and motor learning in PD with a particular focus on beta power. To this end, 20 PD patients (ON medication) and 20 age- and sex-matched HC were trained on a serial reaction time task while neuromagnetic activity was recorded using a 306-channel whole-head MEG system. PD patients showed reduced motor sequence acquisition and were more susceptible to interference by random trials after training on the task as compared to HC. Behavioral differences were paralleled by changes at the neurophysiological level. Diminished sequence acquisition was paralleled by less training-related beta power suppression in motor-cortical areas in PD patients as compared to HC. In addition, PD patients exhibited reduced training-related theta activity in motor-cortical areas paralleling susceptibility to interference. The results support the hypothesis that the acquisition of a new motor sequence relies on suppression of motor-cortical beta oscillations, while motor-cortical theta activity might be related to stabilization of the learned sequence as indicated by reduced susceptibility to interference. Both processes appear to be impaired in PD.

Keywords: Implicit motor learning, Interference, Magnetoencephalography (MEG), Motor control, Oscillatory beta activity, SRTT

NeuroImage. Clinical (2018), Vol. 20 (30128283)

Changes in resting-state directed connectivity in cortico-subcortical networks correlate with cognitive function in Parkinson's disease (2017)

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OBJECTIVE The pathophysiological mechanisms underlying Parkinson's disease (PD)-related cognitive decline and conversion to PD dementia are poorly understood. In the healthy human brain, stable patterns

of posterior-to-anterior cortical information flow have recently been demonstrated in the higher frequency bands using magnetoencephalography (MEG). In this study we estimated PD-related changes in information flow patterns, as well as the contribution of subcortical regions.

METHODS Resting-state MEG recordings were acquired in moderately advanced PD patients (n=34; mean Hoehn and Yahr-stage 2.5) and healthy controls (n=12). MEG signals were projected to both cortical and subcortical brain regions, following which we estimated the balance between incoming and outgoing information flow per region.

RESULTS In PD patients, compared to controls, preferential beta band information outflow was significantly higher for the basal ganglia and frontotemporal cortical regions, and significantly lower for parieto-occipital regions. In addition, in patients, low preferential information outflow from occipital regions correlated with poor global cognitive performance.

CONCLUSION In the PD brain, a shift in balance towards more anterior-to-posterior beta band information flow takes place and is associated with poorer cognitive performance.

SIGNIFICANCE Our results indicate that a reversal of the physiological posterior-to-anterior information flow may be an important mechanism in PD-related cognitive decline.

Keywords: Atlas-based beamforming, Cognition, Directional connectivity, Magnetoencephalography (MEG), Parkinson's disease, Subcortical regions

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2017), Vol. 128, No. 7 (28558317)

The cortical signature of symptom laterality in Parkinson's disease (2017)

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ABSTRACT Patients with Parkinson's disease (PD) often present with unilateral motor symptoms that eventually spread to the other side. This symptom lateralization is diagnostically important, as it serves to distinguish PD from other motor disorders with overlapping symptom profiles. Further, recent studies have shown that the side of symptom onset is important for prognosis, as there are differences in the rate of disease progression and the incidence of secondary symptoms between right- and left-dominant (RD, LD) patients. Physiologically, previous studies have shown asymmetrical decline in structure and metabolism throughout the basal ganglia, although connecting this directly to motor function has been difficult. To identify the neurophysiological basis of symptom laterality in PD, we recorded magnetoencephalography (MEG) during left- and right-hand movement paradigms in patients with PD who exhibited either RD or LD symptomatology. The beta oscillations serving these movements were then imaged using beamforming methods, and we extracted the time series of the peak voxel in the left and right primary motor cortices for each movement. In addition, each patient's symptom asymmetry was quantitated using the Unified Parkinson's Disease Rating Scale (UPDRS), which allowed the relationship between symptom asymmetry and neural asymmetry to be assessed. We found that LD patients had stronger beta suppression during movement, as well as greater post-movement beta rebound compared to patients with RD symptoms, independent of the hand that was moved. Interestingly, the asymmetry of beta activity during right-hand movement uniquely correlated with symptom asymmetry, such that the more LD the symptom profile, the more left-lateralized (i.e., contralateral to movement) the beta response; conversely, the more RD the symptom profile, the more right-lateralized (i.e., ipsilateral to movement) the beta response. This study

is the first to directly probe the relationship between symptom asymmetry and the laterality of neural activity during movement in patients with PD, and suggests that LD patients have a fundamentally different and more "healthy" oscillatory pattern relative to RD patients.

Keywords: Asymmetry, ERD, MEG, Magnetoencephalography, Movement disorders, Oscillations

NeuroImage. Clinical (2017), Vol. 14 (28271041)

Post-traumatic Stress Disorder

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.

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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 recogni-

tion 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)

Post-traumatic stress disorder is associated with altered modulation of prefrontal alpha band oscillations during working memory (2020)

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OBJECTIVE To investigate the relationship between the severity of PTSD symptoms, modulation of alpha band oscillations, and behavioral performance in a working memory task.

METHODS Magnetoencephalography data were recorded in 35 participants with combat exposure and various degrees of PTSD symptom severity while they performed a modified Sternberg working memory task: briefly presented sets of two or six letters had to be held in memory and participants indicated whether subsequent probe letters were present or absent from these sets.

RESULTS PTSD scores were positively correlated with the false positive rate in the high memory load condition. Higher rates of false recognition were associated with negative probes that were seen in recent previous trials (negative probe recency effect) or were physically similar with the list letters. The relative alpha band power in the left middle frontal gyrus was negatively correlated with both PTSD scores and false positive rates.

CONCLUSIONS Reduced task specific modulation of alpha band oscillations in left middle frontal cortex may reflect alterations in the functions of pattern separation and suppression of memory traces for irrelevant or no longer relevant information in PTSD.

SIGNIFICANCE The lower amplitude of prefrontal alpha band oscillations may represent an important physiological basis for core PTSD symptoms and can provide a target for interventions to augment response to treatment.

Keywords: Alpha band oscillations, Magnetoencephalography, Post-traumatic stress disorder, Working memory

Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology (2019), Vol. 130, No. 10 (31408789)

Post-traumatic stress disorder and chronic hyperconnectivity in emotional processing (2019)

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ABSTRACT Post-traumatic stress disorder (PTSD) is associated with heightened responses to threatening stimuli, particularly aggression-related emotional facial expressions. The stability over time of this neurophysiological 'hyperactive' threat response has not been determined. We studied implicit emotional face processing in soldiers with and without PTSD at two time-points (roughly 2 years apart) using magnetoencephalography to determine the response of oscillations and synchrony to happy and angry faces, and the reliability of this marker for PTSD over time. At the initial time-point we had 20 soldiers with and 25 without PTSD; 35 returned for follow-up testing 2 years later, and included 13 with and 22 without PTSD. A mixed-effects analysis was used. There were no significant differences (albeit a slight reduction) in the severity of PTSD between the two time-points. MEG contrasts of the neurophysiological networks involved in the processing of angry vs. happy faces showed that the PTSD group had elevated oscillatory connectivity for angry faces. Maladaptive hypersynchrony in PTSD for threatening faces was seen in subcortical regions, including the thalamus, as well as the ventromedial prefrontal cortex, cingulum gyri, inferior temporal and parietal regions. These results are generally consistent with prior studies and our own, and we demonstrate that this hyperconnectivity was stable over a two year period, in line with essentially stable symptomatology. Together, these results are consistent with the theory that hypervigilance in PTSD is driven by bottom-up, rapid processing of threat-related stimuli that engage a widespread network working in synchrony.

Keywords: Amygdala, Functional connectivity, Implicit emotional face processing, Magnetoencephalography (MEG), Military combat soldiers, Post-traumatic stress disorder, Prefrontal cortex

NeuroImage. Clinical (2018), Vol. 20 (30094169)

Veterans with PTSD demonstrate amygdala hyperactivity while viewing threatening faces: A MEG study (2019)

Badura-Brack, Amy; McDermott, Timothy J; Heinrichs-Graham, Elizabeth; Ryan, Tara J; Khanna, Maya M; Pine, Daniel S; Bar-Haim, Yair; Wilson, Tony W

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ABSTRACT Posttraumatic stress disorder (PTSD) is a major psychiatric disorder that is prevalent in combat veterans. Previous neuroimaging studies have found elevated amygdala activity in PTSD in response to threatening stimuli, but previous work has lacked the temporal specificity to study fast bottom-up fear responses involving the amygdala. Forty-four combat veterans, 28 with PTSD and 16 without, completed psychological testing and then a face-processing task during magnetoencephalography (MEG). The resulting MEG data were pre-processed, transformed into the time-frequency domain, and then imaged using a beamforming approach. We found that veterans with PTSD exhibited significantly stronger oscillatory activity from 50 to 450 ms in the left amygdala compared to veterans without PTSD while processing threatening faces. This group difference was not present while viewing neutral faces. The current study shows that amygdala hyperactivity in response to threatening cues begins quickly in PTSD, which makes theoretical sense as an adaptive bottom-up fear response.

Keywords: Bottom-up, Fear, Magnetoencephalography, Military, Oscillatory activity, Posttraumatic stress

Biological psychology (2018), Vol. 132 (29309826)

Attention training modulates resting-state neurophysiological abnormalities in posttraumatic stress disorder (2019)

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ABSTRACT Recent research indicates the relative benefits of computerized attention control treatment (ACT) and attention bias modification treatment (ABMT) for posttraumatic stress disorder (PTSD); however, neural changes underlying these therapeutic effects remain unknown. This study examines how these two types of attention training modulate neurological dysfunction in veterans with PTSD. A community sample of 46 combat veterans with PTSD participated in a randomized double-blinded clinical trial of ACT versus ABMT and 32 of those veterans also agreed to undergo resting-state magnetoencephalography (MEG) recordings. Twenty-four veterans completed psychological and MEG assessments at pre- and post-training to evaluate treatment effects. MEG data were imaged using an advanced Bayesian reconstruction method and examined using statistical parametric mapping. In this report, we focus on the neural correlates and the differential treatment effects observed using MEG; the results of the full clinical trial have been described elsewhere. Our results indicated that ACT modulated occipital and ABMT modulated medial temporal activity more strongly than the comparative treatment. PTSD symptoms decreased significantly from pre- to post-test. These initial neurophysiological outcome data suggest that ACT modulates visual pathways, while ABMT modulates threat-processing regions, but that both are associated with normalizing aberrant neural activity in veterans with PTSD.

Keywords: Attention training, Cortical, MEG, Magnetoencephalography, PTSD, Treatment

Psychiatry research. Neuroimaging (2018), Vol. 271 (29174765)

Oscillatory magnetic brain activity is related to dissociative symptoms and childhood adversities - A study in women with multiple trauma (2018)

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BACKGROUND Individuals with trauma-related disorders are complex and heterogeneous; part of this complexity derives from additional psychopathology like dissociation as well as environmental adversities such as traumatic stress, experienced throughout the lifespan. Understanding the neurophysiological abnormalities in Post-traumatic stress disorder (PTSD) requires a simultaneous consideration of these factors.

METHODS Resting state magnetoencephalography (MEG) recordings were obtained from 41 women with PTSD and comorbid depressive symptoms, and 16

healthy women. Oscillatory brain activity was extracted for five frequency bands and 11 source locations, and analyzed in relation to shutdown dissociation and adversity-related measures.

RESULTS Dissociative symptoms were related to increased delta and lowered beta power. Adversity-related measures modulated theta and alpha oscillatory power (in particular childhood sexual abuse) and differed between patients and controls.

LIMITATIONS Findings are based on women with comorbid depressive symptoms and therefore may not be applicable for men or groups with other clinical profiles. In respect to childhood adversities, we had no reliable source for the early infancy.

CONCLUSION Trauma-related abnormalities in neural organization vary with both exposure to adversities as well as their potential to evoke ongoing shutdown responses.

Keywords: Childhood adversities, Dissociation, MEG spontaneous activity, PTSD, Trauma

Journal of affective disorders (2017), Vol. 218 (28505586)

Veterans with post-traumatic stress disorder exhibit altered emotional processing and attentional control during an emotional Stroop task (2018)

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BACKGROUND Post-traumatic stress disorder (PTSD) is often associated with attention allocation and emotional regulation difficulties, but the brain dynamics underlying these deficits are unknown. The emotional Stroop task (EST) is an ideal means to monitor these difficulties, because participants are asked to attend to non-emotional aspects of the stimuli. In this study, we used magnetoencephalography (MEG) and the EST to monitor attention allocation and emotional regulation during the processing of emotionally charged stimuli in combat veterans with and without PTSD.

METHOD A total of 31 veterans with PTSD and 20 without PTSD performed the EST during MEG. Three categories of stimuli were used, including combat-related, generally threatening and neutral words. MEG data were imaged in the time-frequency domain and the network dynamics were probed for differences in processing threatening and non-threatening words.

RESULTS Behaviorally, veterans with PTSD were significantly slower in responding to combat-related relative to neutral and generally threatening words. Veterans without PTSD exhibited no significant differences in responding to the three different word types. Neurophysiologically, we found a significant three-way interaction between group, word type and time period across multiple brain regions. Follow-up testing indicated stronger theta-frequency (4-8 Hz) responses in the right ventral prefrontal (0.4-0.8 s) and superior temporal cortices (0.6-0.8 s) of veterans without PTSD compared with those with PTSD during the processing of combat-related words.

CONCLUSIONS Our data indicated that veterans with PTSD exhibited deficits in attention allocation and emotional regulation when processing trauma cues, while those without PTSD were able to regulate emotion by directing attention away from threat.

Keywords: Attention allocation, emotional Stroop task, emotional regulation, oscillation, post-traumatic stress disorder

Psychological medicine (2017), Vol. 47, No. 11 (28478767)

Presurgical Functional Mapping

Timing and type of hemispherectomy for Rasmussen's encephalitis: Analysis of 45 patients (2018)

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OBJECTIVE To describe the surgery outcomes of RE patients in one centerto identify the indication for surgical treatment that results in the most favorable outcome.

METHOD Forty-five RE patients from a single center were retrospectively reviewed. Preoperative evaluations included assessments of clinical manifestations, cognitive status, a physical examination, MRI, positron emission tomography (PET), electroencephalography (EEG), and magnetoencephalography (MEG). The surgical outcomes included seizure outcome, neurological function, EEG, a cognitive evaluation, and antiepileptic drug withdrawal.

RESULTS A total of 45 children (29 male) with RE were included in this study. The mean follow-up period from the first operation was 31.7months (range 6-96). The patients who underwent anatomical hemispherectomy or hemisphere disconnection had better seizure outcomes without greater perioperative complications compared with the patients who underwent functional hemispherectomy. Reoperative hemispherectomy was a safe and effective treatment for patients with postoperative epilepsy recurrence. After the last surgery, 34 patients (74.4%) were evaluated as Engel class I. Most of the patients had favorable neurological outcomes. Analysis revealed that the patientswith IQs greater 70 who underwent operations were more likely to suffer from IQ declines but were also more likely to have higher IQs in the future.

SIGNIFICANCE Compared with functional hemispherectomy and hemisphere disconnection, anatomical hemispherectomy elicited better seizure outcomes with an acceptable level of complications. Early stage operations might lead to better cognitive status, but they are associated with a high risk of IQ decline.

Keywords: Functional outcome, Hemispherectomy, Rasmussen's encephalitis (or Rasmussen encephalitis, RE), Seizure outcome

Epilepsy research (2017), Vol. 132 (28399506)

Schizophrenia

Reduced parietal alpha power and psychotic symptoms: Test-retest reliability of resting-state magnetoencephalography in schizophrenia and healthy controls (2021)

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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)

Intervention-specific patterns of cortical function plasticity during auditory encoding in people with schizophrenia (2021)

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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)

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)

New Graph-Theoretical-Multimodal Approach Using Temporal and Structural Correlations Reveals Disruption in the Thalamo-Cortical Network in Patients with Schizophrenia (2020)

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ABSTRACT Schizophrenia has been understood as a network disease with altered functional and structural connectivity in multiple brain networks compatible to the extremely broad spectrum of psychopathological, cognitive, and behavioral symptoms in this disorder. When building brain networks, functional and structural networks are typically modeled independently: Functional network models are based on temporal correlations among brain regions, whereas structural network models are based on anatomical characteristics. Combining both features may give rise to more realistic and reliable models of brain networks. In this study, we applied a new flexible graph-theoretical-multimodal model called FD (F, the functional connectivity matrix, and D, the structural matrix) to construct brain networks combining functional, structural, and topological information of magnetic resonance imaging (MRI) measurements (structural and resting-state imaging) to patients with schizophrenia (n = 35) and matched healthy individuals (n = 41). As a reference condition, the traditional pure functional connectivity (pFC) analysis was carried out. By using the FD model, we found disrupted connectivity in the thalamo-cortical network in schizophrenic patients, whereas the pFC model failed to extract group differences after multiple comparison correction. We interpret this observation as evidence that the FD model is superior to conventional connectivity analysis, by stressing relevant features of the whole-brain connectivity, including functional, structural, and topological signatures. The FD model can be used in future research to model subtle alterations of functional and structural connectivity, resulting in pronounced clinical syndromes and major psychiatric disorders. Lastly, FD is not limited to the analysis of resting-state functional MRI, and it can be applied to electro-encephalography, magneto-encephalography, etc.

Keywords: dysconnectivity, functional connectivity, resting-state fMRI, schizophrenia, structural connectivity, thalamo-cortical network

Brain connectivity (2019), Vol. 9, No. 10 (31232080)

Relationship between MEG global dynamic functional network connectivity measures and symptoms in schizophrenia (2020)

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ABSTRACT An investigation of differences in dynamic functional network connectivity (dFNC) of healthy controls (HC) versus that of schizophrenia patients (SP) was completed, using eyes-open resting state MEG data. The MEG analysis utilized a source-space activity estimate (MNE/dSPM) whose result was the input to a group spatial independent component analysis (ICA), on which the networks of our MEG dFNC analysis were based. We have previously reported that our MEG dFNC revealed that SP change between brain meta-states (repeating patterns of network correlations which are allowed to overlap in time) significantly more often and to states which are more different, relative to HC. Here, we extend our previous work to investigate the relationship between symptomology in SP and four meta-state metrics. We found a significant correlation between positive symptoms and the two meta-state metrics which showed significant differences between HC and SP. These two statistics quantified 1) how often individuals change state and 2) the total distance traveled within the state-space. We additionally found that a clustering of the meta-state metrics divides SP into groups which vary in symptomology. These results indicate specific relationships between symptomology and brain function for SP.

Keywords: Functional connectivity, Magnetoencephalography, Resting state, Schizophrenia

Schizophrenia research (2019), Vol. 209 (31130399)

Dynamic Functional Network Connectivity in Schizophrenia with Magnetoencephalography and Functional Magnetic Resonance Imaging: Do Different Timescales Tell a Different Story? (2019)

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ABSTRACT The importance of how brain networks function together to create brain states has become increasingly recognized. Therefore, an investigation of eyes-open resting-state dynamic functional network connectivity (dFNC) of healthy controls (HC) versus that of schizophrenia patients (SP) via both functional magnetic resonance imaging (fMRI) and a novel magnetoencephalography (MEG) pipeline was completed. The fMRI analysis used a spatial independent component analysis (ICA) to determine the networks on which the dFNC was based. The MEG analysis utilized a source space activity estimate (minimum norm estimate [MNE]/dynamic statistical parametric mapping [dSPM]) whose result was the input to a spatial ICA, on which the networks of the MEG dFNC were based. We found that dFNC measures reveal significant differences between HC and SP, which depended on the imaging modality. Consistent with previous findings, a dFNC analysis predicated on fMRI data revealed HC and SP remain in different overall brain states (defined by a k-means clustering of network correlations) for significantly different periods of time, with SP spending less time in a highly connected state. The MEG dFNC, in contrast, revealed group differences in more global statistics: SP changed between meta-states (k-means cluster states that are allowed to overlap in time) significantly more often and to states that were more different, relative to HC. MEG dFNC also revealed a highly connected state where a significant difference was observed in interindividual variability, with greater variability among SP. Overall, our results show that fMRI and MEG reveal between-group functional connectivity differences in distinct ways, highlighting the utility of using each of the modalities individually, or potentially a combination of modalities, to better inform our understanding of disorders such as schizophrenia.

Keywords: dynamic functional network connectivity (dFNC), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), schizophrenia

Brain connectivity (2019), Vol. 9, No. 3 (30632385)

Attenuated Post-Movement Beta Rebound Associated With Schizotypal Features in Healthy People (2020)

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INTRODUCTION Schizophrenia and schizotypal personality disorder (SPD) lie on a single spectrum of mental illness and converging evidence suggests similarities in the etiology of the 2 conditions. However, schizotypy is a heterogeneous facet of personality in the healthy population and so may be seen as a bridge between health and mental illness. Neural evidence for such a continuity would have implications for the characterization and treatment of schizophrenia. Based on our previous work identifying a relationship between symptomology in schizophrenia and abnormal movement-induced electrophysiological response (the post-movement beta rebound [PMBR]), we predicted that if subclinical schizotypy arises from similar neural mechanisms to schizophrenia, schizotypy in healthy individuals would be associated with reduced PMBR.

METHODS One-hundred sixteen participants completed a visuomotor task while their neural activity was recorded by magnetoencephalography. Partial correlations were computed between a measure of PMBR extracted from left primary motor cortex and scores

on the Schizotypal Personality Questionnaire (SPQ), a self-report measure of schizotypal personality. Correlations between PMBR and SPQ factor scores measuring cognitive-perceptual, interpersonal and disorganization dimensions of schizotypy were also computed. Effects of site, age, and sex were controlled for.

RESULTS We found a significant negative correlation between total SPQ score and PMBR. This was most strongly mediated by variance shared between interpersonal and disorganization factor scores.

CONCLUSION These findings indicate a continuum of neural deficit between schizotypy and schizophrenia, with diminution of PMBR, previously reported in schizophrenia, also measurable in individuals with schizotypal features, particularly disorganization and impaired interpersonal relations.

Keywords: individual differences, magnetoencephalography, psychosis, schizophrenia, schizotypal personality disorder, schizotypy

Schizophrenia bulletin (2019), Vol. 45, No. 4 (30239878)

MEG resting-state oscillations and their relationship to clinical symptoms in schizophrenia (2019)

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ABSTRACT Neuroimaging studies suggest that schizophrenia is characterized by disturbances in oscillatory activity, although at present it remains unclear whether these neural abnormalities are driven by dimensions of symptomatology. Examining different subgroups of patients based on their symptomatology is thus very informative in understanding the role of neural oscillation patterns in schizophrenia. In the present study we examined whether neural oscillations in the delta, theta, alpha, beta and gamma bands correlate with positive and negative symptoms in individuals with schizophrenia (SZ) during rest. Resting-state brain activity of 39 SZ and 25 neurotypical controls was recorded using magnetoencephalography. Patients were categorized based on the severity of their positive and negative symptoms. Spectral analyses of beamformer data revealed that patients high in positive symptoms showed widespread low alpha power, and alpha power was negatively correlated with positive symptoms. In contrast, patients high in negative symptoms showed greater beta power in left hemisphere regions than those low in negative symptoms, and beta power was positively correlated with negative symptoms. We further discuss these findings and suggest that different neural mechanisms may underlie positive and negative symptoms in schizophrenia.

Keywords: Alpha band, Beta band, MEG, Negative symptoms, Neural oscillations, Positive symptoms, Resting-state, Schizophrenia

NeuroImage. Clinical (2018), Vol. 20 (30238919)

Evoked Potentials Investigations of Deficit Versus Nondeficit Schizophrenia: EEG-MEG Preliminary Data (2020)

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ABSTRACT Heterogeneity of schizophrenia is a major obstacle toward understanding the disorder. One likely subtype is the deficit syndrome (DS) where patients suffer from predominantly negative symptoms. This study investigated the evoked responses and the evoked magnetic fields to identify the neurophysiological deviations associated with the DS. Ten subjects were recruited for each group (Control, DS, and Nondeficit schizophrenia [NDS]). Subjects underwent magnetoencephalography (MEG) and electroencephalography (EEG) testing while listening to an oddball paradigm to generate the P300 as well as a paired click paradigm to generate the mid-latency auditory-evoked responses (MLAER) in a sensory gating paradigm. MEG-coherence source imaging (CSI) during P300 task revealed a significantly higher average coherence value in DS than NDS subjects in the gamma band (30-80 Hz), when listening to standard stimuli but only NDS subjects had a higher average coherence level in the gamma band than controls when listening to the novel sounds. P50, N100, and P3a ERP amplitudes (EEG analysis) were significantly decreased in NDS compared with DS subjects. The data suggest that the deviations in the 2 patient groups are qualitatively different. Deviances in NDS patients suggest difficulty in both early (as in the gating paradigm), as well as later top-down processes (P300 paradigm). The main deviation in the DS group was an exaggerated responsiveness to ongoing irrelevant stimuli detected by EEG whereas NDS subjects had an exaggerated response to novelty.

Keywords: N100, P200, P300, P50, coherence source imaging, sensory gating

Clinical EEG and neuroscience (2019), Vol. 50, No. 2 (30175598)

Associations and Heritability of Auditory Encoding, Gray Matter, and Attention in Schizophrenia (2020)

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BACKGROUND Auditory encoding abnormalities, gray-matter loss, and cognitive deficits are all candidate schizophrenia (SZ) endophenotypes. This study evaluated associations between and heritability of auditory network attributes (function and structure) and attention in healthy controls (HC), SZ patients, and unaffected relatives (UR).

METHODS Whole-brain maps of M100 auditory activity from magnetoencephalography recordings, cortical thickness (CT), and a measure of attention were obtained from 70 HC, 69 SZ patients, and 35 UR. Heritability estimates (h2r) were obtained for M100, CT at each group-difference region, and the attention measure.

RESULTS SZ patients had weaker bilateral superior temporal gyrus (STG) M100 responses than HC and a weaker right frontal M100 response than UR. Abnormally large M100 responses in left superior frontal gyrus were observed in UR and SZ patients. SZ patients showed smaller CT in bilateral STG and right frontal regions. Interrelatedness between 3 putative SZ endophenotypes was demonstrated, although in the left STG the M100 and CT function-structure associations observed in HC and UR were absent in SZ patients. Heritability analyses also showed that right frontal M100 and bilateral STG CT measures are significantly heritable.

CONCLUSIONS Present findings indicated that the 3 SZ endophenotypes examined are not isolated markers of pathology but instead are connected. The pattern of auditory encoding group differences and the pattern of brain function-structure associations differ as a function of brain region, indicating the need for regional specificity when studying these endophenotypes, and

with the presence of left STG function-structure associations in HC and UR but not in SZ perhaps reflecting disease-associated damage to gray matter that disrupts function-structure relationships in SZ.

Keywords: M100, MEG, attention, auditory, gray matter, heritability, schizophrenia

Schizophrenia bulletin (2019), Vol. 45, No. 4 (30099543)

Changes in electrophysiological markers of cognitive control after administration of galantamine (2019)

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ABSTRACT The healthy brain is able to maintain a stable balance between bottom-up sensory processing and top-down cognitive control. The neurotransmitter acetylcholine plays a substantial role in this. Disruption of this balance could contribute to symptoms occurring in psychosis, including subtle disruption of motor control and aberrant appropriation of salience to external stimuli; however the pathological mechanisms are poorly understood. On account of the role beta oscillations play in mediating cognitive control, investigation of beta oscillations is potentially informative about such mechanisms. Here, we used magnetoencephalography to investigate the effect of the acetylcholinesterase-inhibitor, galantamine, on beta oscillations within the sensorimotor region during both a sensorimotor task and a relevance-modulation task in healthy participants, employing a double blind randomized placebo controlled cross-over design. In the galantamine condition, we found a significant reduction in the post-movement beta rebound in the case of executed movements and also in a planned but not executed movement. In the latter case, the effect was significantly greater following task-relevant compared with irrelevant stimuli. The results suggest that the action of galantamine reduces the influence of top-down cognitive processing relative to bottom-up perceptual processing in a manner resembling changes previously reported in schizophrenia.

Keywords: Acetylcholine, Beta oscillations, Magnetoencephalography, PMBR, Schizophrenia

NeuroImage. Clinical (2018), Vol. 20 (30090697)

Neuroimaging investigations of dorsal stream processing and effects of stimulus synchrony in schizophrenia (2019)

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ABSTRACT Impairments in auditory and visual processing are common in schizophrenia (SP). In the unisensory realm visual deficits are primarily noted for the dorsal visual stream. In addition, insensitivity to timing offsets between stimuli are widely reported for SP. The aim of the present study was to test at the physiological level differences in dorsal/ventral stream visual processing and timing sensitivity between SP and healthy controls (HC) using MEG and a simple auditory/visual task utilizing a variety of multisensory conditions. The paradigm included all combinations of synchronous/asynchronous and central/peripheral stimuli, yielding 4 task conditions. Both HC and SP groups showed activation in parietal areas (dorsal visual stream) during all multisensory conditions, with parietal areas showing decreased activation for SP relative to HC, and a significantly delayed peak of activation for SP in intraparietal sulcus (IPS). We also observed a differential effect of stimulus synchrony on HC and SP parietal response. Furthermore, a (negative) correlation was found between SP positive symptoms and activity in IPS. Taken

together, our results provide evidence of impairment of the dorsal visual stream in SP during a multisensory task, along with an altered response to timing offsets between presented multisensory stimuli.

Keywords: Dorsal visual stream, Magnetoencephalography, Multisensory integration, Parietal lobe, Schizophrenia, Visual field

Psychiatry research. Neuroimaging (2018), Vol. 278 (29884441)

Identifying auditory cortex encoding abnormalities in schizophrenia: The utility of low-frequency versus 40 Hz steady-state measures (2019)

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ABSTRACT Magnetoencephalography (MEG) and EEG have identified poststimulus low frequency and 40 Hz steady-state auditory encoding abnormalities in schizophrenia (SZ). Negative findings have also appeared. To identify factors contributing to these inconsistencies, healthy control (HC) and SZ group differences were examined in MEG and EEG source space and EEG sensor space, with better group differentiation hypothesized for source than sensor measures given greater predictive utility for source measures. Fifty-five HC and 41 chronic SZ were presented 500 Hz sinusoidal stimuli modulated at 40 Hz during simultaneous whole-head MEG and EEG. MEG and EEG source models using left and right superior temporal gyrus (STG) dipoles estimated trial-to-trial phase similarity and percent change from prestimulus baseline. Group differences in poststimulus low-frequency activity and 40 Hz steady-state response were evaluated. Several EEG sensor analysis strategies were also examined. Poststimulus low-frequency group differences were observed across all methods. Given an age-related decrease in left STG 40 Hz steady-state activity in HC (HC > SZ), 40 Hz steady-state group differences were evident only in younger participants' source measures. Findings thus indicated that optimal data collection and analysis methods depend on the auditory encoding measure of interest. In addition, whereas results indicated that HC and SZ auditory encoding low-frequency group differences are generally comparable across modality and analysis strategy (and thus not dependent on obtaining construct-valid measures of left and right auditory cortex activity), 40 Hz steady-state group-difference findings are much more dependent on analysis strategy, with 40 Hz steady-state source-space findings providing the best group differentiation.

Keywords: auditory encoding, electroencephalography, magnetoencephalography, schizophrenia, superior temporal gyrus

Psychophysiology (2018), Vol. 55, No. 8 (29570815)

Magnetoencephalography reveals an increased non-target P3a, but not target P3b, that is associated with high non-clinical psychosocial deficits (2019)

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ABSTRACT Auditory processing deficits are frequently identified in autism and schizophrenia, and the two

disorders have been shown to share psychosocial difficulties. This study used magnetoencephalography to investigate auditory processing differences for those with a high degree of a non-clinical autistic and schizotypal trait phenotype, Social Disorganisation (SD). Participants were 18 low (9 female) and 19 high (9 female) SD scorers (18-40 years) who completed a three-stimulus auditory oddball paradigm of speech sounds (standard: 100ms 'o', deviant: 150ms 'o', novel: 150ms 'e'). Spatio-temporal cluster analysis revealed increased amplitude for the high SD group in a left ($p = 0.006$) and a right ($p = 0.020$) hemisphere cluster in response to the novel non-target. No cluster differences were found in response to the target deviant. These findings suggest that those with a high degree of the SD phenotype recruit more cortical resources when processing unattended, novel speech stimuli, which may lead to psychosocial deficits.

Keywords: Auditory oddball, Autism, P300, Schizotypy, Social Disorganisation

Psychiatry research. Neuroimaging (2018), Vol. 271 (29182941)

Dissociable auditory mismatch response and connectivity patterns in adolescents with schizophrenia and adolescents with bipolar disorder with psychosis: A magnetoencephalography study (2018)

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BACKGROUND There is overlap between schizophrenia and bipolar disorder regarding genetic risk as well as neuropsychological and structural brain deficits. Finding common and distinct event-response potential (ERP) responses and connectivity patterns may offer potential biomarkers to distinguish the disorders.

OBJECTIVE To examine the neuronal auditory response elicited by a roving mismatch negativity (MMN) paradigm using magnetoencephalography (MEG).

PARTICIPANTS 15 Adolescents with schizophrenia (ASZ), 16 adolescents with bipolar disorder with psychosis (ABP), and 14 typically developing individuals (TD) METHODS: The data were analysed using time-series techniques and dynamic causal modelling (DCM).

OUTCOME MEASURES MEG difference wave (deviant - standard) at primary auditory (~90ms), MMN (~180ms) and long latency (~300ms).

RESULTS The amplitude of difference wave showed specific patterns at all latencies. Most notably, it was significantly reduced ABP compared to both controls and ASZ at early latencies. In contrast, the amplitude was significantly reduced in ASZ compared to both controls and ABP. The DCM analysis showed differential connectivity patterns in all three groups. Most notably, inter-hemispheric connections were strongly dominated by the right side in ASZ only.

CONCLUSIONS Dissociable patterns of the primary auditory response and MMN response indicate possible developmentally sensitive, but separate biomarkers for schizophrenia and bipolar disorder.

Keywords: Biomarker, Bipolar disorder, Connectivity, First episode, Mismatch negativity, Schizophrenia

Schizophrenia research (2018), Vol. 193 (28760539)

Magnetoencephalographic and functional MRI connectomics in schizophrenia via intra- and inter-network connectivity (2018)

Houck, Jon M; Çetin, Mustafa S; Mayer, Andrew R; Bustillo, Juan R; Stephen, Julia; Aine, Cheryl; Cañive, Jose; Perrone-Bizzozero, Nora; Thoma, Robert J; Brookes, Matthew J; Calhoun, Vince D

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ABSTRACT Examination of intrinsic functional connectivity using functional MRI (fMRI) has provided important findings regarding dysconnectivity in schizophrenia. Extending these results using a complementary neuroimaging modality, magnetoencephalography (MEG), we present the first direct comparison of functional connectivity between schizophrenia patients and controls, using these two modalities combined. We developed a novel MEG approach for estimation of networks using MEG that incorporates spatial independent component analysis (ICA) and pairwise correlations between independent component timecourses, to estimate intra- and intern-network connectivity. This analysis enables group-level inference and testing of between-group differences. Resting state MEG and fMRI data were acquired from a large sample of healthy controls (n=45) and schizophrenia patients (n=46). Group spatial ICA was performed on fMRI and MEG data to extract intrinsic fMRI and MEG networks and to compensate for signal leakage in MEG. Similar, but not identical spatial independent components were detected for MEG and fMRI. Analysis of functional network connectivity (FNC; i.e., pairwise correlations in network (ICA component) timecourses) revealed a differential between-modalities pattern, with greater connectivity among occipital networks in fMRI and among frontal networks in MEG. Most importantly, significant differences between controls and patients were observed in both modalities. MEG FNC results in particular indicated dysfunctional hyperconnectivity within frontal and temporal networks in patients, while in fMRI FNC was always greater for controls than for patients. This is the first study to apply group spatial ICA as an approach to leakage correction, and as such our results may be biased by spatial leakage effects. Results suggest that combining these two neuroimaging modalities reveals additional disease-relevant patterns of connectivity that were not detectable with fMRI or MEG alone.

Keywords: Functional connectivity, Imaging, MEG, Resting state connectivity, Schizophrenia

NeuroImage (2017), Vol. 145, No. Pt A (27725313)

Stroke

Central auditory processing in adults with chronic stroke without hearing loss: A magnetoencephalography study (2021)

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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)

Modulation of Motor Cortical Activities by Action Observation and Execution in Patients with Stroke: An MEG Study (2020)

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ABSTRACT Action observation therapy has recently attracted increasing attention; however, the mechanisms through which action observation and execution (AOE) modulate neural activity in stroke patients remain unclear. This study was aimed at investigating the effects of action observation and two types of AOE on motor cortical activations after stroke using magnetoencephalography. Twenty patients with stroke and 20 healthy controls were recruited for the collection of data on the beta oscillatory activity in the primary motor cortex (M1). All participants performed the conditions of resting, observation only, and video observation combined with execution (video AOE). Stroke patients performed one additional condition of affected hand observation combined with execution (affected hand AOE). The relative change index of beta oscillations was calculated, and nonparametric tests were used to examine the differences in conditions. In stroke patients, the relative change index of M1 beta oscillatory activity under the video AOE condition was significantly lower than that under the observation only and affected hand AOE conditions. Moreover, M1 cortical activity did not significantly differ under the observation only and affected hand AOE conditions. For healthy controls, the relative change index under the video AOE condition was significantly lower than that under the observation only condition. In addition, no significant differences in relative change indices were found under the observation only and video AOE conditions between the 2 groups. This study provides new insight into the neural mechanisms underlying AOE, which supports the use of observing videos of normal movements during action observation therapy in stroke rehabilitation.

Neural plasticity (2019), Vol. 2019 (31781183)

Acute Phase Neuronal Activity for the Prognosis of Stroke Recovery (2020)

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ABSTRACT Strokes causing similar lesions and clinical states can be followed by diverse regains of neurological functions, indicating that the clinical recovery can depend on individual modulating factors. A promising line to disclose these factors, to finally open new therapeutic strategies, is to search for individual indices of recovery prognosis. Here, we pursued on strengthening the value of acute phase electrophysiological biomarkers for poststroke functional recovery in a wide group of patients. We enrolled 120 patients affected by a monohemispheric stroke within the middle cerebral artery territory (70 left and 50 right damages) and collected the NIH stroke scale (NIHSS) score in the acute phase (T0, median 4 days) and chronic follow-up (T1, median 6 months). At T0, we executed electrophysiological noninvasive assessment (19-channel electroencephalography (EEG) or 28 channels per side magnetoencephalography (MEG)) of brain activity at rest by means of band powers in the contra- and ipsilesional hemispheres (CLH, ILH) or the homologous area symmetry (HArS). Low-band (2-6 Hz) HArS entered the regression model for predicting the stabilized clinical state ($p < 0.001$), with bilateral impairment correlated with a poor outcome. Present data strengthen the fact that low-band impairment of homologous ipsi- and contralesional hemispheric regions in the acute stroke indicate a negative prognosis of clinical recovery.

Neural plasticity (2019), Vol. 2019 (31611914)

Recovery of the 20 Hz Rebound to Tactile and Proprioceptive Stimulation after Stroke (2018)

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ABSTRACT Sensorimotor integration is closely linked to changes in motor-cortical excitability, observable in the modulation of the 20 Hz rhythm. After somatosensory stimulation, the rhythm transiently increases as a rebound that reflects motor-cortex inhibition. Stroke-induced alterations in afferent input likely affect motor-cortex excitability and motor recovery. To study the role of somatosensory afferents in motor-cortex excitability after stroke, we employed magnetoencephalographic recordings (MEG) at 1-7 days, one month, and 12 months in 23 patients with stroke in the middle cerebral artery territory and 22 healthy controls. The modulation of the 20 Hz motor-cortical rhythm was evaluated to two different somatosensory stimuli, tactile stimulation, and passive movement of the index fingers. The rebound strengths to both stimuli were diminished in the acute phase compared to the controls and increased significantly during the first month after stroke. However, only the rebound amplitudes to tactile stimuli fully recovered within the follow-up period. The rebound strengths in the affected hemisphere to both stimuli correlated strongly with the clinical scores across the follow-up. The results show that changes in the 20 Hz rebound to both stimuli behave similarly and occur predominantly during the first month. The 20 Hz rebound is a potential marker for predicting motor recovery after stroke.

Neural plasticity (2018), Vol. 2018 (29681928)

Randomized trial of transcranial direct current stimulation for poststroke dysphagia (2019)

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OBJECTIVE We evaluated whether transcranial direct current stimulation (tDCS) is able to enhance dysphagia rehabilitation following stroke. Besides relating clinical effects with neuroplastic changes in cortical swallowing processing, we aimed to identify factors influencing treatment success.

METHODS In this double-blind, randomized study, 60 acute dysphagic stroke patients received contralesional anodal (1mA, 20 minutes) or sham tDCS on 4 consecutive days. Swallowing function was thoroughly assessed before and after the intervention using the validated Fiberoptic Endoscopic Dysphagia Severity Scale (FEDSS) and clinical assessment. In 10 patients, swallowing-related brain activation was recorded applying magnetoencephalography before and after the intervention. Voxel-based statistical lesion pattern analysis was also performed.

RESULTS Study groups did not differ according to demographic data, stroke characteristics, or baseline dysphagia severity. Patients treated with tDCS showed greater improvement in FEDSS than the sham group (1.3 vs 0.4 points, mean difference = 0.9, 95% confidence interval [CI] = 0.4-1.4, $p < 0.0005$). Functional recovery was accompanied by a significant increase of activation ($p < 0.05$) in the contralesional swallowing network after real but not sham tDCS. Regarding predictors of treatment success, for every hour earlier that treatment was initiated, there was greater improvement on the FEDSS (adjusted odds ratio = 0.99, 95% CI = 0.98-1.00, $p < 0.05$) in multivariate analysis. Stroke location in the right insula and operculum was indicative of worse response to tDCS ($p < 0.05$).

INTERPRETATION Application of tDCS over the contralesional swallowing motor cortex supports swallowing network reorganization, thereby leading to faster rehabilitation of acute poststroke dysphagia. Early treatment initiation seems beneficial. tDCS may be less effective in right-hemispheric insulo-opercular stroke. Ann Neurol 2018;83:328-340.

Annals of neurology (2018), Vol. 83, No. 2 (29350775)

Strength of ~20-Hz Rebound and Motor Recovery After Stroke (2017)

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BACKGROUND Stroke is a major cause of disability worldwide, and effective rehabilitation is crucial to regain skills for independent living. Recently, novel therapeutic approaches manipulating the excitatory-inhibitory balance of the motor cortex have been introduced to boost recovery after stroke. However, stroke-induced neurophysiological changes of the motor cortex may vary despite of similar clinical symptoms. Therefore, better understanding of excitability changes after stroke is essential when developing and targeting novel therapeutic approaches.

OBJECTIVE AND METHODS We identified recovery-related alterations in motor cortex excitability after stroke using magnetoencephalography. Dynamics (suppression and rebound) of the ~20-Hz motor cortex rhythm were monitored during passive movement of the index finger in 23 stroke patients with upper limb paresis at acute phase, 1 month, and 1 year after stroke.

RESULTS After stroke, the strength of the ~20-Hz rebound to stimulation of both impaired and healthy hand was decreased with respect to the controls in the affected (AH) and unaffected (UH) hemispheres, and increased during recovery. Importantly, the rebound strength was lower than that of the controls in the AH and UH also to healthy-hand stimulation despite of intact afferent input. In the AH, the rebound strength to impaired-hand stimulation correlated with hand motor recovery.

CONCLUSIONS Motor cortex excitability is increased bilaterally after stroke and decreases concomitantly with recovery. Motor cortex excitability changes are related to both alterations in local excitatory-inhibitory circuits and changes in afferent input. Fluent sensorimotor integration, which is closely coupled with excitability changes, seems to be a key factor for motor recovery.

Keywords: beta rhythm, motor cortex excitability, passive movement, proprioception, stroke recovery

Neurorehabilitation and neural repair (2017), Vol. 31, No. 5 (28164736)

Traumatic Brain Injuries

Local and large-scale beta oscillatory dysfunction in males with mild traumatic brain injury (2021)

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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 thalamocortical 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

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Typical and Aberrant Functional Brain Flexibility: Lifespan Development and Aberrant Organization in Traumatic Brain Injury and Dyslexia

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ABSTRACT Intrinsic functional connectivity networks derived from different neuroimaging methods and connectivity estimators have revealed robust developmental trends linked to behavioural and cognitive maturation. The present study employed a dynamic functional connectivity approach to determine dominant intrinsic coupling modes in resting-state neuromagnetic data

from 178 healthy participants aged 8-60 years. Results revealed significant developmental trends in three types of dominant intra- and inter-hemispheric neuronal population interactions (amplitude envelope, phase coupling, and phase-amplitude synchronization) involving frontal, temporal, and parieto-occipital regions. Multi-class support vector machines achieved 89% correct classification of participants according to their chronological age using dynamic functional connectivity indices. Moreover, systematic temporal variability in functional connectivity profiles, which was used to empirically derive a composite flexibility index, displayed an inverse U-shaped curve among healthy participants. Lower flexibility values were found among age-matched children with reading disability and adults who had suffered mild traumatic brain injury. The importance of these results for normal and abnormal brain development are discussed in light of the recently proposed role of cross-frequency interactions in the fine-grained coordination of neuronal population activity.

Keywords: brain maturation, cross-frequency coupling, magnetoencephalography, reading disability, resting-state activity, traumatic brain injury

Brain sciences (2019), Vol. 9, No. 12 (31888230)

Marked Increases in Resting-State MEG Gamma-Band Activity in Combat-Related Mild Traumatic Brain Injury (2021)

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)

Mild Traumatic Brain Injury Affects Cognitive Processing and Modifies Oscillatory Brain Activity during Attentional Tasks (2020)

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ABSTRACT Despite the high prevalence of mild traumatic brain injury (mTBI), current diagnostic tools to objectively assess cognitive complaints after mTBI continue to be inadequate. Our aim was to identify neuronal correlates for cognitive difficulties in mTBI patients by evaluating the possible alterations in oscillatory brain activity during a behavioral task known to be sensitive to cognitive impairment after mTBI. We compared oscillatory brain activity during rest and cognitive tasks (Paced Auditory Serial Addition Test [PASAT] and a vigilance test [VT]) with magnetoencephalography between 25 mTBI patients and 20 healthy controls. Whereas VT induced no significant differences compared with resting state in either group, patients exhibited stronger attenuation of 8- to 14-Hz oscillatory activity during PASAT than healthy controls in the left parietotemporal cortex ($p \leq 0.05$). Further, significant task-related modulation in the left superior frontal gyrus and right prefrontal cortex was detected only in patients. The 10-Hz (alpha) peak frequency declined in frontal, temporal, and parietal regions during PASAT compared with rest ($p < 0.016$) in patients, whereas in controls it remained the same or showed a tendency to increase. In patients, the 10-Hz peak amplitude was negatively correlated with behavioral performance in the Trail Making Test. The observed alterations in the cortical oscillatory activity during cognitive load may provide measurable neurophysiological correlates of cognitive difficulties in mTBI patients, even at the individual level.

Keywords: alpha frequency modulation, cognitive task, magnetoencephalography, mild traumatic brain injury

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Theta-Band Oscillations as an Indicator of Mild Traumatic Brain Injury (2019)

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ABSTRACT Mild traumatic brain injury (mTBI) patients continue to pose a diagnostic challenge due to their diverse symptoms without trauma-specific changes in structural imaging. We addressed here the possible early changes in spontaneous oscillatory brain activity after mTBI, and their feasibility as an indicator of injury in clinical evaluation. We recorded resting-state magnetoencephalography (MEG) data in both eyes-open and eyes-closed conditions from 26 patients (11 females and 15 males, aged 20-59) with mTBI 6 days-6 months after the injury, and compared their spontaneous oscillatory activity to corresponding data from 139 healthy controls. Twelve of the patients underwent a follow-up measurement at 6 months. Ten of all patients were without structural lesions in MRI. At single-subject level, aberrant 4-7 Hz (theta) band activity exceeding the + 2 SD limit of the healthy subjects was visible in 7 out of 26 patients; three out of the seven patients with abnormal theta activity were without any detectable lesions in MRI. Of the patients that participated in the follow-up measurements, five showed abnormal theta activity in the first recording, but only two in the second measurement. Our results suggest that aberrant theta-band oscillatory activity can provide an early objective sign of brain dysfunction after mTBI. In 3/7 patients, the slow-wave activity was transient and visible only in the first recording, urging prompt timing for the measurements in clinical settings.

Keywords: Low frequency activity, Magnetoencephalography (MEG), Oscillations, Repeated measurements, Resting-state, Traumatic brain injury (TBI)

Brain topography (2018), Vol. 31, No. 6 (30097835)

Default Mode Network Oscillatory Coupling Is Increased Following Concussion

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ABSTRACT Concussion is a common form of mild traumatic brain injury. Despite the descriptor "mild," a single injury can leave long-lasting and sustained alterations to brain function, including changes to localized activity and large-scale interregional communication. Cognitive complaints are thought to arise from such functional deficits. We investigated the impact of injury on neurophysiological and functionally specialized resting networks, known as intrinsic connectivity networks (ICNs), using magnetoencephalography. We assessed neurophysiological connectivity in 40 males, 20 with concussion and 20 without. Regions-of-interest that comprise nodes of ICNs were defined, and their time courses derived using a beamformer approach. Pairwise fluctuations and covariations in band-limited amplitude envelopes were computed reflecting measures of functional connectivity. Intra-network connectivity was compared between groups using permutation testing and correlated with symptoms. We observed increased resting spectral connectivity in the default mode network (DMN) and motor networks (MOTs) in our concussion group when compared with controls, across alpha through gamma ranges. Moreover, these differences were not explained by power spectrum density within the ICNs. Furthermore, this increased coupling was significantly associated with symptoms in the DMN and MOTs-but once accounting for comorbidities (including, depression, anxiety, and ADHD) only the DMN continued to be associated with symptoms. The DMN plays a critical role in shifting between cognitive tasks. These data suggest even a single concussion can perturb the intrinsic coupling of this functionally specialized network in the brain, and may explain persistent and wide-ranging symptomatology.

Keywords: concussion, functional connectivity, magnetoencephalography, mild traumatic brain injury, neural oscillations, resting-state, synchrony

Frontiers in neurology (2018), Vol. 9 (29755402)

MEG Working Memory N-Back Task Reveals Functional Deficits in Combat-Related Mild Traumatic Brain Injury (2020)

Huang, Ming-Xiong; Nichols, Sharon; Robb-Swan, Ashley; Angeles-Quinto, Annemarie; Harrington, Deborah L; Drake, Angela; Huang, Charles W; Song, Tao; Diwakar, Mithun; Risbrough, Victoria B; Matthews, Scott; Clifford, Royce; Cheng, Chung-Kuan; Huang, Jeffrey W; Sinha, Anusha; Yurgil, Kate A; Ji, Zhengwei; Lerman, Imanuel; Lee, Roland R; Baker, Dewleen G

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ABSTRACT Combat-related mild traumatic brain injury (mTBI) is a leading cause of sustained cognitive impairment in military service members and Veterans. However, the mechanism of persistent cognitive deficits in-

cluding working memory (WM) dysfunction is not fully understood in mTBI. Few studies of WM deficits in mTBI have taken advantage of the temporal and frequency resolution afforded by electromagnetic measurements. Using magnetoencephalography (MEG) and an N-back WM task, we investigated functional abnormalities in combat-related mTBI. Study participants included 25 symptomatic active-duty service members or Veterans with combat-related mTBI and 20 healthy controls with similar combat experiences. MEG source-magnitude images were obtained for alpha (8-12 Hz), beta (15-30 Hz), gamma (30-90 Hz), and low-frequency (1-7 Hz) bands. Compared with healthy combat controls, mTBI participants showed increased MEG signals across frequency bands in frontal pole (FP), ventromedial prefrontal cortex, orbitofrontal cortex (OFC), and anterior dorsolateral prefrontal cortex (dlPFC), but decreased MEG signals in anterior cingulate cortex. Hyperactivations in FP, OFC, and anterior dlPFC were associated with slower reaction times. MEG activations in lateral FP also negatively correlated with performance on tests of letter sequencing, verbal fluency, and digit symbol coding. The profound hyperactivations from FP suggest that FP is particularly vulnerable to combat-related mTBI.

Keywords: blast brain injury, frontal pole, magnetoencephalography, traumatic brain injury, working memory

Cerebral cortex (New York, N.Y.: 1991) (2019), Vol. 29, No. 5 (29668852)

Altered Rich-Club and Frequency-Dependent Subnetwork Organization in Mild Traumatic Brain Injury: A MEG Resting-State Study

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ABSTRACT Functional brain connectivity networks exhibit "small-world" characteristics and some of these networks follow a "rich-club" organization, whereby a few nodes of high connectivity (hubs) tend to connect more densely among themselves than to nodes of lower connectivity. The Current study followed an "attack strategy" to compare the rich-club and small-world network organization models using Magnetoencephalographic (MEG) recordings from mild traumatic brain injury (mTBI) patients and neurologically healthy controls to identify the topology that describes the underlying intrinsic brain network organization. We hypothesized that the reduction in global efficiency caused by an attack targeting a model's hubs would reveal the "true" underlying topological organization. Connectivity networks were estimated using mutual information as the basis for cross-frequency coupling. Our results revealed a prominent rich-club network organization for both groups. In particular, mTBI patients demonstrated hyper-synchronization among rich-club hubs compared to controls in the δ band and the δ-γ1, θ-γ1, and β-γ2 frequency pairs. Moreover, rich-club hubs in mTBI patients were overrepresented in right frontal brain areas, from θ to γ1 frequencies, and underrepresented in left occipital regions in the δ-β, δ-γ1, θ-β, and β-γ2 frequency pairs. These findings indicate that the rich-club organization of resting-state MEG, considering its role in information integration and its vulnerability to various disorders like mTBI, may have a significant predictive value in the development of reliable biomarkers to help the validation of the recovery from mTBI. Furthermore, the proposed approach might be used as a validation tool to assess patient recovery.

Keywords: cross-frequency coupling, intrinsic networks, magnetoencephalography (MEG), mild traumatic brain injury, network resilience

Frontiers in human neuroscience (2017), Vol. 11 (28912698)

Data-Driven Topological Filtering Based on Orthogonal Minimal Spanning Trees: Application to Multigroup Magnetoencephalography Resting-State Connectivity (2018)

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ABSTRACT In the present study, a novel data-driven topological filtering technique is introduced to derive the backbone of functional brain networks relying on orthogonal minimal spanning trees (OMSTs). The method aims to identify the essential functional connections to ensure optimal information flow via the objective criterion of global efficiency minus the cost of surviving connections. The OMST technique was applied to multichannel, resting-state neuromagnetic recordings from four groups of participants: healthy adults (n = 50), adults who have suffered mild traumatic brain injury (n = 30), typically developing children (n = 27), and reading-disabled children (n = 25). Weighted interactions between network nodes (sensors) were computed using an integrated approach of dominant intrinsic coupling modes based on two alternative metrics (symbolic mutual information and phase lag index), resulting in excellent discrimination of individual cases according to their group membership. Classification results using OMST-derived functional networks were clearly superior to results using either relative power spectrum features or functional networks derived through the conventional minimal spanning tree algorithm.

Keywords: brain networks, network topology, optimization of information flow, resting state, topological filtering

Brain connectivity (2017), Vol. 7, No. 10 (28891322)

Activation of dominant hemisphere association cortex during naming as a function of cognitive performance in mild traumatic brain injury: Insights into mechanisms of lexical access (2018)

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ABSTRACT Patients with a history of mild traumatic brain injury (mTBI) and objective cognitive deficits frequently experience word finding difficulties in normal conversation. We sought to improve our understanding of this phenomenon by determining if the scores on standardized cognitive testing are correlated with measures of brain activity evoked in a word retrieval task (confrontational picture naming). The study participants (n = 57) were military service members with a history of mTBI. The General Memory Index (GMI) determined after administration of the Rivermead Behavioral Memory Test, Third Edition, was used to assign subjects to three groups: low cognitive performance (Group 1: GMI ≤ 87, n = 18), intermediate cognitive performance (Group 2: 88 ≤ GMI ≤ 99, n = 18), and high cognitive performance (Group 3: GMI ≥ 100, n = 21). Magnetoencephalography data were recorded while participants named eighty pictures of common objects. Group differences in evoked cortical activity were observed relatively early (within 200 ms from picture onset) over a distributed network of left hemisphere cortical regions including the fusiform gyrus, the entorhinal and parahippocampal cortex, the supramarginal gyrus and posterior part of the superior temporal gyrus, and the inferior frontal and rostral middle frontal gyri. Differences were also present in bilateral cingulate cortex and paracentral lobule, and in the right fusiform gyrus. All differences reflected a lower amplitude of the evoked responses for Group 1 relative to Groups 2 and 3. These findings may indicate weak afferent inputs to and within an extended cortical network including association cortex of the dominant hemi-

sphere in patients with low cognitive performance. The association between word finding difficulties and low cognitive performance may therefore be the result of a diffuse pathophysiological process affecting distributed neuronal networks serving a wide range of cognitive processes. These findings also provide support for a parallel processing model of lexical access.

Keywords: Attractor dynamics, Lexical retrieval, Magnetoencephalography, Picture naming, Traumatic brain injury

NeuroImage. Clinical (2017), Vol. 15 (28702351)

Reconfiguration of dominant coupling modes in mild traumatic brain injury mediated by δ-band activity: A resting state MEG study (2018)

Antonakakis, Marios; Dimitriadis, Stavros I; Zervakis, Michalis; Papanicolaou, Andrew C; Zouridakis, George

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ABSTRACT During the last few years, rich-club (RC) organization has been studied as a possible brain-connectivity organization model for large-scale brain networks. At the same time, empirical and simulated data of neurophysiological models have demonstrated the significant role of intra-frequency and inter-frequency coupling among distinct brain areas. The current study investigates further the importance of these couplings using recordings of resting-state magnetoencephalographic activity obtained from 30 mild traumatic brain injury (mTBI) subjects and 50 healthy controls. Intra-frequency and inter-frequency coupling modes are incorporated in a single graph to detect group differences within individual rich-club subnetworks (type I networks) and networks connecting RC nodes with the rest of the nodes (type II networks). Our results show a higher probability of inter-frequency coupling for (δ-γ1), (δ-γ2), (θ-β), (θ-γ2), (α-γ2), (γ1-γ2) and intra-frequency coupling for (γ1-γ1) and (δ-δ) for both type I and type II networks in the mTBI group. Additionally, mTBI and control subjects can be correctly classified with high accuracy (98.6%), whereas a general linear regression model can effectively predict the subject group using the ratio of type I and type II coupling in the (δ, θ), (δ, β), (δ, γ1), and (δ, γ2) frequency pairs. These findings support the presence of an RC organization simultaneously with dominant frequency interactions within a single functional graph. Our results demonstrate a hyperactivation of intrinsic RC networks in mTBI subjects compared to controls, which can be seen as a plausible compensatory mechanism for alternative frequency-dependent routes of information flow in mTBI subjects.

Keywords: brain network models, cross-frequency coupling, intrinsic networks, magnetoencephalography (MEG), mild traumatic brain injury (mTBI)

Neuroscience (2017), Vol. 356 (28576727)

Contrasting Effects of Posttraumatic Stress Disorder and Mild Traumatic Brain Injury on the Whole-Brain Resting-State Network: A Magnetoencephalography Study (2017)

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ABSTRACT The aim of this study was to evaluate alterations in whole-brain resting-state networks associated with posttraumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI). Networks were constructed from locations of peak statistical power on an individual basis from magnetoencephalography (MEG) source series data by applying the weighted phase lag index and surrogate data thresholding procedures. Networks representing activity in the alpha bandwidth as well as wideband activity (DC-80 Hz) were created. Statistical comparisons were adjusted for age and education level. Alpha network results demonstrate reductions in network structure associated with PTSD, but no differences associated with mTBI. Wideband network results demonstrate a shift in connectivity from the alpha to theta bandwidth in both PTSD and mTBI. Also, contrasting alterations in network structure are noted, with increased randomness associated with PTSD and increased structure associated with mTBI. These results demonstrate the potential of the analysis of MEG resting-state networks to differentiate two highly comorbid conditions. The importance of the alpha bandwidth to resting-state connectivity is also highlighted, while demonstrating the necessity of considering activity in other bandwidths during network construction.

Keywords: brain networks, graph theory, magnetoencephalography, posttraumatic stress disorder, traumatic brain injury

Brain connectivity (2017), Vol. 7, No. 1 (28006976)

Resting-State Magnetoencephalography Reveals Different Patterns of Aberrant Functional Connectivity in Combat-Related Mild Traumatic Brain Injury (2018)

Huang, Ming-Xiong; Harrington, Deborah L; Robb Swan, Ashley; Angeles Quinto, Annemarie; Nichols, Sharon; Drake, Angela; Song, Tao; Diwakar, Mithun; Huang, Charles W; Risbrough, Victoria B; Dale, Anders; Bartsch, Hauke; Matthews, Scott; Huang, Jeffrey W; Lee, Roland R; Baker, Dewleen G

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ABSTRACT Blast mild traumatic brain injury (mTBI) is a leading cause of sustained impairment in military service members and veterans. However, the mechanism of persistent disability is not fully understood. The present study investigated disturbances in brain functioning in mTBI participants using a source-imaging-based approach to analyze functional connectivity (FC) from resting-state magnetoencephalography (rs-MEG). Study participants included 26 active-duty service members or veterans who had blast mTBI with persistent post-concussive symptoms, and 22 healthy control active-duty service members or veterans. The source time courses from regions of interest (ROIs) were used to compute ROI to whole-brain (ROI-global) FC for different frequency bands using two different measures: 1) time-lagged cross-correlation and 2) phase-lock synchrony. Compared with the controls, blast mTBI participants showed increased ROI-global FC in beta, gamma, and low-frequency bands, but not in the alpha band. Sources of abnormally increased FC included the: 1) prefrontal cortex (right ventromedial prefrontal cortex [vmPFC], right rostral anterior cingulate cortex [rACC]), and left ventrolateral and dorsolateral prefrontal cortex; 2) medial temporal lobe (bilateral parahippocampus, hippocampus, and amygdala); and 3) right putamen and cerebellum. In contrast, the blast mTBI group also

showed decreased FC of the right frontal pole. Group differences were highly consistent across the two different FC measures. FC of the left ventrolateral prefrontal cortex correlated with executive functioning and processing speed in mTBI participants. Altogether, our findings of increased and decreased regionalpatterns of FC suggest that disturbances in intrinsic brain connectivity may be the result of multiple mechanisms, and are associated with cognitive sequelae of the injury.

Keywords: FC, MEG, TBI, blast brain injury, excitation, inhibition

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