BRAIN & MIND SYMPOSIUM 2023

ABSTRACTS

P1. Investigating the role of heparan sulfate in schizophrenia

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Heparan sulfate (HS) is a polysaccharide that regulates a wide range of biological functions in in animal tissues. In the brain, HS participates in activities such as synaptic development, function and pruning. These processes are also known to be dysregulated in psychiatric disorders. Using induced pluripotent stem cell (iPSC) -derived neurons from patients with schizophrenia, we have recently found a broad downregulation of enzymes involved in HS biosynthesis in the affected neurons suggesting the role of HS in the development of the disorder. To illuminate the role of HS in synaptic development in schizophrenia, we designed a co-culture model of donor-specific iPSC-derived neurons and rat astrocytes to promote synaptic maturation. We performed immunocytochemistry (ICC) on the co-cultures to study the expression patterns of HS across time. Using cell lines from affected and unaffected individuals, we found a peak in the expression of HS synthesizing enzyme HS3ST3 at 4-5 weeks in vitro coinciding with the establishment of synaptic connections. Next, to further investigate HS expression in these cells, we aim to study the expression of 3-O-sulfated HS due to its specific role in fine-tuning synaptic connections and interactions with complement proteins, events which could be correlated with the synaptic abnormalities evident in schizophrenia affected individuals.

P2. Spatially resolved glioblastoma Invadome identifies neurodevelopmental pathway reprogramming

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Dissemination of invasive glioblastoma cells in the brain complicates neurosurgery and poses a critical threat for the long-term survival of patients. In addition to their extreme motility, glioblastoma cells are a moving target for therapies as they dynamically adapt their phenotypic states in response to drugs, changes in gene expression or extracellular cues. In order to draw a comprehensive map of the glioblastoma invasion (Invadome), we screened the dynamics of the invasive cells' transcriptome, activated kinase pathways and drug sensitivity in patient-derived xenografts, fresh patient biopsies and patient databases. Bulk, single-cell RNA sequencing and spatial transcriptomics (Visium) data revealed that glioblastoma cells of the Neuron-Precursor Cell (NPC)-like subtype aggressively invade the brain parenchyma in vivo. Identification of activated pathways in live cell extracts using the Pamgene technology, pinpointed specific networks of activated kinases. Interestingly, dysfunction of these pathways has been previously associated with neurodevelopmental defects, including neuron progenitors' migration and differentiation. Using high-throughput drug screening, we also identified specific vulnerabilities of the invasive/NPC -like glioblastoma cells. In preclinical studies, we demonstrated that some of these FDA-approved, blood-brain-barrier permeable drugs could eradicate invasive glioblastomas without adverse effects.

P3. Insights on the mechanism of action of NMDA receptor blocker ketamine

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Ketamine is an N-methyl-D-aspartate receptor (NMDAR) blocking dissociative anesthetic and rapid-acting antidepressant. The antidepressant effects emerge at sub-anesthetic doses which are associated with paradoxical cortical excitation and glutamate release. Preclinical evidence suggests that the acute increase in glutamatergic neuron activity is mediated by local disinhibitory effect - however, the mechanistic basis of this phenomenon is unclear. We are carrying out research aiming to elucidate the role of NMDAR antagonism and disinhibition for ketamine's effects using in silico, in vitro and in vivo methods. Specifically, we are performing all-atom molecular dynamics simulations to understand how S- and R-ketamine interact with open NMDAR. Further, we utilize optical electrophysiology tools and microelectrode array recordings to investigate dose-dependent effects of ketamine on pyramidal and GABAergic neuron firing in primary cortical neuron cultures, with the aim to gain mechanistic insights on the interplay between neuronal networks and ketamine. The status of this project is presented in this work.

P4. Exploring the role of RNA methylation in synaptic plasticity and hippocampus-dependent learning through the application of novel pharmacological tools

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m6A methylation is the predominant eukaryotic mRNA modification, pivotal in the epitranscriptomic regulation of various cellular processes. Recent research has highlighted its significance in neuronal signalling and memory formation. However, the precise mechanisms by which it modulates neuronal circuits involved in memory encoding remain elusive. Moreover, m6A methylation changes have been linked to neurodevelopmental and neurodegenerative conditions. Consequently, drugs modulating this process could be invaluable in treating neurological disorders marked by memory deficits. This project aims to elucidate the impact of novel pharmacological agents targeting m6A methylation on hippocampal neuronal circuits integral to spatial learning and memory in rodents. A multifaceted approach encompassing electrophysiology, histology, and behavioral assays will be employed to discern how altering the m6A methylation apparatus influences excitatory synaptic transmission, long-term plasticity, and hippocampus-reliant learning and memory in these animals. Concurrently using diverse m6A-targeting drugs will pave the way for innovative m6A-centric pharmacotherapies. The second phase of this research will evaluate if manipulating m6A methylation can ameliorate pathological phenotypes in disease models. The most promising agent, chosen based on initial findings, will be trialed on the 5xFAD mouse model of Alzheimer's disease, known for early spatial learning and hippocampal synaptic plasticity anomalies. Additionally, the chronic restraint stress model will be utilized to gauge the drugs' efficacy against stress-induced anxiety-like behaviors. In both scenarios, electrophysiological evaluations of hippocampal synaptic transmission and plasticity will be conducted alongside behavioral tests. Ultimately, this endeavor aims to demystify m6A methylation's role in memory and cerebral function, aspiring to discover novel therapeutic avenues for memory-centric neurological ailments.

P5. Absence of GluK1 kainate receptors from PV+ interneurons leads to perturbed amygdala circuit function, hyperactivity and fear of novelty

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Parvalbumin expressing (PV+) interneurons are key players in the local inhibitory circuits and their developmental maturation coincides with the onset of adult-type network dynamics in the brain. Glutamatergic signaling regulates emergence of the unique PV+ neuron phenotype, yet the receptor mechanisms involved are not fully understood. Specifically, recent work has implicated the importance of GluK1 type kainate receptors (KARs) in altering the maturation cortical interneurons and modulating the function of PV+ interneurons in the amygdala. Here we show that GluK1 is necessary for PV+ interneuron neurochemical maturation. Loss of GluK1 from PV+ led to amygdala circuit dysfunction, namely diminished glutamatergic drive and stronger feedforward inhibition onto amygdala principal neurons, as well as attenuation of long-term potentiation (LTP). Behaviorally, the absence of GluK1 from PV+

interneurons associated with hyperactivity and increased fear of novelty. These results provide valuable new evidence for the critical role of GluK1 KARs in the development and maturation of PV+ interneurons and amygdala circuitry.

P6. GluK1 kainate receptors are necessary for functional maturation of parvalbumin interneurons

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Constituting the largest subpopulation of cortical interneurons (~40%), parvalbumin (PV) interneurons play a myriad of crucial roles in encephalic functions. PV interneurons are key players in the local inhibitory circuits and their developmental maturation coincides with the onset of adult-type network dynamics in the brain. Interestingly, PV interneurons are also the most vulnerable population of interneurons. Glutamatergic signalling regulates emergence of the unique PV+ neuron phenotype, yet the receptor mechanisms involved are not fully understood Here I show that GluK1 subunit containing Kainate receptors (KARs) are necessary for development and maintenance of the excitability and functional properties of PV+ interneurons in the basolateral amygdala (BLA). Ablation of GluK1 expression specifically from PV+ neurons resulted in the loss of their characteristic high firing rate throughout development and furthermore, alterations of their electrophysiological signatures. In addition, we observed reduced spontaneous excitatory synaptic activity at adult GluK1 lacking PV+ neurons. Intriguingly, knockdown of GluK1 expression from adult PV+ neurons was sufficient to abolish the PV+ phenotype, suggesting a role for GluK1 in dynamic regulation of PV+ neuron maturation state. These results indicate a critical role for GluK1 KARs in regulation of PV+ interneuron function across development and suggest GluK1 as a potential therapeutic target for pathologies involving PV+ neuron malfunction.

P7. Impact of early life stress on limbic microcircuitry and specific types of interneurons

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Early life stress is a known risk factor for the development of psychopathological states in adulthood, demonstrated both in humans and in animal models. The function of the limbic system, particularly of the amygdala and hippocampus is strongly altered under stressful conditions, but the detailed mechanisms of those alterations at the level of microcircuits and specific cell types remain to be elucidated. Here I investigated the changes in the activity of the GABAergic interneurons induced by the limited bedding and nesting model of early life stress applied from P4 to P14 in mice. Animals put through limited bedding and nesting conditions develop an anxiety-like phenotype and learning defects in parallel with morphological changes in the limbic circuitry. My results show that stress exposure via limited bedding and nesting model is associated with sex-dependent changes in the physiological functions of the parvalbumin and somatostatin interneurons, resulting in altered excitation/inhibition balance in the lateral amygdala – the

physiological hallmark of aberrant fear-related behaviors. More specifically, I observed a shift in the intrinsic excitability of both interneuronal types and a reduction of the excitatory inputs of these cells. These data support that stress-induced changes in interneuron activity drive the circuit malfunction contributing to anxiety-like behaviors.

P8. Role of kainate receptors in the development of mouse striatum

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Kainate receptors belong to the family of ionotropic glutamate receptors. They have predominant functions in modulation of neurotransmitter release and neuronal excitability, but also mediate ionotropic postsynaptic responses at certain synapses. Genetic disruption of all five kainate receptor subunits reduces cortico-striatal synaptic connectivity and leads to obsessive-compulsive disorder-related pathological behavior. It is not known yet which subunit of kainate receptors is responsible for the pathological phenotype. We hypothesized that GluK1-containing kainate-type glutamate receptors (GluK1) are important for the proper development of the cortico-striatal connections, and deletion of GluK1 may be responsible for the repetitive behavior seen in five subunit knockout animals. To test this hypothesis, we evaluated the expression of GluK1 during the development of the cortico-striatal circuitry using immunohistochemistry and assessed if GluK1-containing receptors regulate cortico-striatal synaptic transmission by electrophysiology. We have shown that during the early postnatal development GluK1 subunit is expressed in cortical neurons, which innervate striatum. In the adult animals, expression of GluK1 in pyramidal cells is significantly decreased. In developing, but not adult striatal medium spiny neurons (MSNs) pharmacological activation of GluK1 increases the frequency of spontaneous glutamatergic synaptic currents. Interestingly, GluK1 agonist does not affect the frequency of miniature synaptic events and short-term synaptic plasticity in developing MSNs. We can conclude that GluK1-containing receptors, expressed by layer V pyramidal cells, increase the efficiency of cortico-striatal synaptic contacts during the restricted period of brain development by unknown mechanism, not involving the release probability of glutamate at these synapses.

P9. Elfn1 regulates inputs differentially to the cholinergic neurons of the striatum and deletion of Elfn1 contributes to ADHD like phenotype

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Cell adhesion molecules are a group of proteins that allow neurons to recognize correct partners to form synapses with and help in forming/regulating these connections. This is important for proper circuit forming during development and problems in it can lead to a wide variety of diseases. One such protein is Elfn1, a member of the leucine rich protein family which has been linked previously to different

neurodevelopmental diseases such as ADHD. Striatum is considered to be important for motor learning and attention, and dysfunctions in striatal circuitry have been linked to ADHD. From our own preliminary data and single cell transcriptomics database we know that Elfn1 is expressed by the cholinergic neurons (ChINs) of striatum. The goal of our study is to find out how Elfn1 affects the development of striatal circuitry, focusing on ChINs.   We created a mice line that has conditionally knockout Elfn1 specifically from the ChlNs. From RNA scope we learned that it is expressed by only ChINs of the striatum and that expression was present in one week old animals. KO animals showed no expression of protein and even heterozygous animals showed decreased levels of expression. In our electrophysiological data, thalamic inputs showed no change in short-term plasticity either in neonatal or juvenile animals. However, in juvenile animals' deletion of Elfn1 turns short-term facilitation of the cortical inputs to non-faciliatory. This suggests that Elfn1 might act in the input specific manner in ChINs. In our behavioral experiments KO and heterozygous animals expressed hyperactive phenotype in the new environment, which was then rescued to normal levels by amphetamine injections. Additionally, these animal groups also showed deficits in motor learning in the rota- rod test.   From our results it seems like Elfn1 is regulating synapses in input specific way and that deletion of Elfn1 was able to evoke ADHD-like phenotype in the animals.

P10. Rodent in vivo imaging and electrophysiology platform at the Neuroscience Center, HiLife

Anastasia Ludwig

Neuroscience center, HiLIFE

Rodent In Vivo Imaging and Electrophysiology Platform provides cutting-edge approaches and services for in vivo imaging and electrophysiology in both anesthetized and awake behaving mice. When combined with pharmacological and genetic manipulations, or with electrical, chemogenetic, and optogenetic stimulation of specific neuronal populations, these techniques support ground–breaking fundamental and preclinical research in neuroscience and brain disorders.

P11. Controlling visually-guided behavior of mice in real time in closed–loop Quantum Behavior experiments

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Vision at low light levels offers a unique possibility to link behavioral performance in freely-moving mice to the quantized information arising from sparse photons in retinal inputs. However, previous behavioral experiments have relied on spatially fixed dim light increment or decrement stimuli in a water maze in darkness or in dim background light (Quantum Behavior). Here we combine Quantum Behavior experiments with closed-loop stimulus control. Our aim is to control mouse swimming trajectories by closed-loop visual stimuli in conditions, where correlating retinal coding and behavioral performance is feasible. The mice were trained to associate a stimulus light in a six-armed water maze with a submerged platform at the end of one corridor. After training, we began the closed-loop stimulus control

experiments. We followed the head position and orientation of a mouse in real time using our deep-learning based tracker running at 50 frames per second on videos recorded in IR light (940 nm). Detected head position was then used in real time to control the activation of light spots located at the end of each maze corridor. We used three distinct stimulus sequences to demonstrate that we can significantly confine the swimming trajectories of freely-moving mice to particular patterns in a water maze. Quantum Behavior experiments with closed-loop stimulus control open up at least two exciting future avenues in visual neuroscience: 1) it allows mapping of neural decisions across neural scales from the retina to freely-moving mouse behavior while controlling in real time the amount of visual information arising from sparse photons in retinal inputs, 2) in combination with higher-order brain activity measurements and manipulations, our paradigm could open a possibility to link behavioral decisions to neural activity patterns and quantized visual information in retinal space.

P12. The hippocampal audio editor – neural correlates of event segmentation in an auditory narrative

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Event segmentation structures our experience as well as our memories, and the ability to retain a memory of an event requires an intact hippocampus. It has previously been shown that the event boundary elicits an fMRI activation peak in the hippocampus, and it has been proposed that these responses represent a high-level, modality-independent process of "printing out" the event model to memory. However, the studies up to date have been conducted on audio-visual narratives, and as the hippocampus is also known to take part in visual relational processing, it is not altogether certain that the peak activity is, in fact, high-level and modality independent. This study addresses the question by investigating hippocampal responses to event boundaries in an auditory narrative that is entirely without a visual component. The stimulus was a 71-minute-long audio book, and it was segmented behaviourally by a separate group of participants with a naïve intuitive segmentation paradigm. The fMRI data from 50 participants was analysed with a region of interest (ROI) analysis in the hippocampus, as well as in an exploratory manner on all areas from a cortical atlas. The hippocampus was found to respond significantly to event boundaries in the story. Strong responses were also found in areas of the posterior medial cortex (PMC), as well as in ventromedial prefrontal cortex (vmPFC), parahippocampal gyrus, anterior cingulate (ACC) and the insula. Many of these are known to be involved in representing the event model, and some with switching between internal and external processing modes. In conclusion, the hippocampus does detect and respond to event boundaries in a naturalistic auditory narrative, which is in line with the "print out" hypothesis and implies that these activations are related to domain-general episodic encoding.

P13. Adults with ADHD present large-scale decreased functional connectivity during spatial and verbal working memory tasks

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Background: Attention deficit hyperactivity disorder (ADHD) symptoms are thought to arise from wide-spread abnormalities in connections between brain areas. However, only few studies have examined whole-brain networks in adults with ADHD. Individuals with ADHD commonly exhibit difficulties in working memory, a higher-order cognitive function activating multiple brain areas. In our study, we aimed to identify working-memory related functional networks differentiating adults with and without ADHD. Methods: 41 adults with ADHD and 35 neurotypical controls conducted spatial and verbal n-back working memory tasks during functional magnetic resonance imaging. Functional connectivity was determined as correlations of the time-series between all pairs of brain areas, resulting in whole-brain functional connectivity network. Network Based Statistic method was then used to distinguish subnetworks, or communities of connections, indicating group differences. Results: Adults with ADHD presented decreased functional connectivity during both working memory tasks in networks encompassing frontal, parietal, temporal and occipital cerebral cortices, cerebellum and subcortical structures. Conclusions: Our results suggest that adults with ADHD have wide-spread aberrancies in functional synchronization between several distinct brain areas.

P14. Earlobe electrical stimulation enhances the effect of paired associative stimulation more than auricular vagus nerve stimulation

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Paired associative stimulation (PAS) has been used to induce spinal1 and cortical plasticity. It combines a low frequency transcranial magnetic stimulation (TMS) with peripheral electrical nerve stimulation (PNS). TMS induces neuronal activity in motor cortical circuits and the pyramidal tract, whereas PNS induces activation in somatosensory afferents. PAS with high frequency PNS (100Hz) induces a stable potentiation of motor evoked potential (MEP) amplitudes in healthy subjects. We have studied High PAS on incomplete spinal cord injured patients, resulting increase in independence and improved motor function. Non-invasive auricular vagus nerve stimulation (aVNS) has been applied for therapeutical approaches. Motor improvements likely result from VNS activated LTP-like plasticity. 10 participants received 4 stimulation sessions in random order: PAS, PAS & aVNS, PAS & shamVNS, aVNS. Participants were blinded to the stimulation sequence. VNS was delivered below perceptual threshold. MEP amplitudes were measured before, post, post 30min, post60min and post90min of the stimulation At baseline there was no difference in MEP amplitudes between groups. All PAS sessions increased MEP amplitudes significantly. PAS increased MEP amplitudes by 22%. PAS+aVNS increased MEP values by 33% across all time points; the difference compared to PAS alone was not significant. Unexpectedly, PAS+shamVNS increased MEP amplitudes, significantly more than PAS alone (p = 0.001, Kendall's W = 0.212). aVNS alone increased MEP amplitudes by 8%. Combining electrical earlobe stimulation with PAS might enhance MEP potentiation and increase cortical and spinal excitability. A trend for MEP enhancement was observed with transcutaneous auricular VNS. Additional experiments are needed to define the connection between the great auricular nerve, that innervates earlobe, and spinal cord excitability, and to better understand the effects of using earlobe as a sham target for aVNS.

P15. Real-time EEG-based spike detection for suppression of epileptic activity with TMS

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Epilepsy is one of the most common neurological disorders. In epilepsy, some parts of the cortex are hyperexcitable, causing pathological bursts of electrical activity called spikes in the electroencephalogram (EEG). Delivery of repetitive transcranial magnetic stimulation (rTMS) timed to physiologic EEG rhythms has been shown to modulate excitability. We posit that consistently delivering TMS pulses during spikes could enhance rTMS treatment for epilepsy by effectively suppressing the epileptic activity. Thus, we prepared an EEG-guided pipeline for timing TMS based on real-time spike detection. A convolutional neural network model was trained to classify 120-ms segments of EEG as spike or non-spike activity. The training data was constructed from an EEG recording containing 292 spikes (annotated by human expert), from a patient with self-limited epilepsy with centrotemporal spikes. The trained model was implemented in Python and integrated into an in-house real-time EEG-guided TMS pipeline. The model classifies the ongoing EEG every 10 ms. If an EEG segment is classified as a spike, a trigger signal is sent to the TMS device. The real-time implementation was tested by streaming into the software another EEG recording, which was from the same patient and included 282 spikes. A spike was classified as detected if a trigger was sent within 300 ms from the start of the spike activity. The pipeline detected 52% of the spikes with an average latency of 115 ms between the start of the spike and the trigger. Only 6% of the triggers were erroneous, i.e., unrelated to spike activity. The pipeline thus allows timing TMS based on observed spikes with high specificity. The sensitivity of the implementation and the consistency of the TMS–trigger latency should still be improved. Our pipeline enables a wide variety of TMS–EEG experiments, including EEG-triggered stimulation, to be conducted on epilepsy patients, with the goal of optimally reducing epileptic activity with TMS.

P16. Optimization of TMS—EEG target for biomarker development using MRI priors

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Brain disorders, especially psychiatric conditions, are notoriously difficult to treat and diagnose as we often lack objective quantifiers beyond behavioral assessment. A powerful tool for identification of neurophysiological biomarkers for such conditions is transcranial magnetic stimulation (TMS) in combination with electroencephalography (EEG). While TMS—EEG has vast potential, it is challenging to produce biomarkers with sufficient predictive power due to high interindividual variability and presence

of artifacts. These challenges can be mitigated by individually optimizing the stimulation target, ensuring that the data accurately represents genuine neuronal response to TMS. We propose a pipeline for TMS—EEG data collection that takes the first step towards standardization of personalized TMS—EEG measures to ensure reproducible results for diagnostic purposes. Anatomical, diffusion, and functional magnetic resonance imaging (MRI) are utilized to localize the cortical areas belonging to the affected brain networks, increasing specificity of collected data. Then, the TMS—EEG mapping is used to iteratively optimize the target location for a more reliable brain response, reflecting direct activation of neuronal circuits by TMS. To demonstrate the benefit of the method, we collected TMS—EEG data from 11 healthy volunteers. The left dorsolateral prefrontal cortex was stimulated in accordance with our pipeline, followed by a fully standardized clinical Beam F3 protocol, utilized in rTMS treatments for major depressive disorder. Our method resulted in improved data quality, revealed by enhanced early TMS response amplitudes indicative of cortical reactivity, decreased presence of muscle and decay artifacts, and an increased signal-to-noise ratio. The proposed protocol proves the feasibility of the emerging field of TMS—EEG biomarkers; however, it is at present limited by its dependence on neurophysiological expertise, which constrains its immediate clinical applicability

P17. Accuracy of estimating EEG phase for brain state-dependent TMS inside an MRI device

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State-dependent stimulation of the brain is a promising approach for research and treatment of brain disorders. Recent studies have shown that the phase of electroencephalographic (EEG) signals can influence corticospinal responses, e.g., to transcranial magnetic stimulation (TMS). Because of EEG's limited sensitivity to subcortical structures, combining EEG with functional magnetic resonance imaging (fMRI) for brain stimulation could be valuable for studying brain dynamics at high spatiotemporal resolution. Nevertheless, conducting EEG within the MRI environment poses challenges due to electromagnetic interference. Here, we assess the feasibility of EEG phase-triggered brain stimulation inside MRI, using carbon-wire loops (CWL) to suppress electromagnetic artifacts. We studied 10 subjects (8 from van der Meer et al. 2016). In brief, reference EEG was recorded outside MRI, and the recordings were repeated inside MRI. The EEG cap was equipped with CWLs that recorded bipolar signals. Gradient artifacts were suppressed with a template subtraction method, and subsequently motion-induced artifacts were regressed out leveraging CWL measurements. A surface Laplacian centered on the C3 electrode was applied to isolate the sensorimotor mu rhythm. In addition, one experiment with real-time EEG processing was conducted. Real-time-estimated phases were compared with phases estimated post-hoc using the approach of Zrenner et al. (2020). Artifact-suppressed EEG showed an error of −8.5o ± 69.7o between estimated and ground-truth phase angles across all subjects. The obtained results are consistent with previous studies using the same phase estimation methodology, indicating that the phase estimation is accurate. Despite the challenge of achieving accurate EEG phase estimation during an fMRI measurement, the proposed artifact-suppression and phase-estimation pipeline shows significant promise in enabling real-time EEG-triggered brain stimulation combined with fMRI.

P18. Effect of stimulus orientation in paired-pulse Transcranial Magnetic Stimulation protocols on the spatial activation of forearm muscles

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Introduction Transcranial magnetic stimulation (TMS) can probe both inhibitory and excitatory mechanisms in human motor cortex. In paired-pulse TMS (ppTMS), a sub-threshold conditioning stimulus (CS) precedes a supra-threshold test stimulus (TS) with an inter-stimulus interval (ISI). Motor cortex's overlapping muscle representations make individual muscle excitability assessment challenging with commercial coils. We investigate the effect of stimulus orientation and ISI on forearm muscles' spatial activation. Methods Twelve healthy volunteers participated. We used multi-locus TMS (mTMS) [1] with NBS neuronavigation system (Nexstim, Finland). Motor evoked potentials (MEPs) were recorded using high-density surface electromyography device (HDsEMG; LISiN, Italy) from the right forearm muscles. We determined motor hotspot, optimal stimulus orientation (0°), and resting motor threshold (rMT) for the flexor carpi radialis muscle. We applied ppTMS with 0.5 and 8 ms ISIs, with CS at 0° and 90° (90% rMT), and TS at 0° (110% rMT). Results Activation maps were derived from median peak-to-peak MEP amplitude across trials. The two CS orientations resulted in different MEP amplitude distribution maps on the forearm muscles (p<0.001). The centroid of peak MEP amplitude in averaged spatial distribution maps differed significantly among subjects in these four protocols in the proximal-distal (p=0.009) and the medial-lateral (p=0.02) directions. Conclusion Inhibitory and excitatory ppTMS protocols and CS orientation lead to distinct MEP spatial distributions over forearm muscles. Changing CS orientation by 90° from optimal diminishes both inhibitory and facilitatory effects. Changes in the centroid location in the MEP activation maps can indicate the recruitment of different neuronal populations associated with distinct muscles. Combining mTMS with HD-sEMG can provide new insights into the corticospinal pathways' activation. References [1] Souza, V. H. et al. Brain Stimul. 15, (2022)

P19. Cortical activity networks at birth correlate with 2-year neurodevelopment in infants with perinatal asphyxia

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Abstract Background: Perinatal asphyxia, often leading to hypoxic-ischaemic encephalopathy (HIE), is a major cause of neurodevelopmental disorders. While infants with moderate or severe HIE suffer high mortality and morbidity, less is known of those with perinatal asphyxia without HIE or only mild HIE. Here, we set out to study this population by evaluating whether cortical activity networks derived from early postnatal EEG recordings correlate with 2-year neurodevelopment measured with Griffiths III standardized developmental assessment. Methods: We used 19 channel EEG data from a clinical cohort of infants (N = 36). EEG network metrics were evaluated for each frequency, signal pair, and sleep state. Amplitude-amplitude correlations (AACs) were computed by taking Pearson correlation coefficient

between mutually orthogonalized signals, whereas phase-phase correlations (PPCs) were computed using phase lag index between phase time series. Finally, we correlated AACs and PPCs with Griffiths III developmental assessment done at 2-years of age. Results: PPCs in quiet sleep correlated significantly with Fine Motor scores in all frequencies except alpha (p < 0.05 in 5-15% of signal pairs). AACs in active sleep correlated significantly with Griffiths III Fine Motor scores in all frequencies except low delta (p < 0.05 in 4-28% of signal pairs).   Conclusion: We show that network metrics extracted from neonatal EEG correlate with 2-year neurodevelopment in infants with perinatal asphyxia. Although our work is limited by cohort size, these findings hold promise for using network metrics derived from early EEG as a biomarker for prognostic assessment in this cohort.

P20. Acute social stress induces slow-wave sleep and promotes high-frequency EEG activity: an experimental study

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Evidence of the impact of chronic stress on sleep is abundant, yet experimental sleep studies with a focus on acute stress are scarce and the results are mixed. Our study aimed to fill this gap by experimentally investigating the effects of pre-sleep social stress on sleep EEG in the subsequent night. Thirty-four healthy individuals (65% females, Mage=25.76 years SD=3.35) underwent a stress-inducing (SC) or neutral control condition (CC) in virtual reality (VR). Overnight EEG measurements were used to analyze sleep architecture and power spectral density (PSD) across the sleep cycles. We measured heart rate variability (HRV), skin electrodermal activity (EDA), and salivary cortisol to capture physiological arousal during the VR task and the pre-sleep period. The effect of the stress task was observed in physiological parameters. Following acute stress (SC), the amount of slow-wave sleep (SWS) was higher and N2 sleep lower relative to CC. This effect was emphasized in the first sleep cycle. In SC, PSD was elevated in the beta-low (16-24Hz) and beta-high (25-35Hz) frequency ranges during SWS over the entire night. An experience of acute social stress induced longer duration of SWS in the subsequent sleep period, especially in early sleep. A similar homeostatic effect towards restorative sleep is well-evidenced in animal stress studies but has not been previously reported in experimental human studies. Furthermore, acute social stress promoted high-frequency PSD during SWS, suggesting that transient stress may exert similar effects as reported in chronic stress and human insomnia studies.

P21. Improving source estimation of retinotopic MEG responses with joint analysis of multiple subjects

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Commonly used solutions for the MEG inverse problem operate on data from individuals, but combining the measurements of multiple subjects have been suggested to increase the spatial resolution. We compared three multi-subject solutions on a retinotopic mapping dataset of 20 subjects. Increasing the subject count from 1 to 10 reduced the median peak activation–V1 distances by 5–15% compared to the single-subject results. The observed peak activation locations also comply better with established retinotopic maps of the primary visual cortex with increasing subject counts. Our results suggest that higher spatial accuracy can be achieved by pooling data from multiple subjects.

P22. Automatic remnant magnetic field compensation using OPM sensors and biplanar electromagnetic coils

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OPMs sufficiently sensitive to MEG require a near-zero magnetic field to operate. Passive shields consisting of layers of μ-metal and aluminium are able to suppress most of the ambient magnetic fields. However, even 100-nT remnant DC-field can be found inside a passive shield, which the internal coils of an OPM sensor may have a problem compensating. This remnant field is typically well characterized by the three homogenous fields and the five independent first-order gradients. Therefore, electromagnetic coils that generate these field components can be used to efficiently compensate the remnant field. We designed such biplanar coils using the bfieldtools software package [1,2] and manually wound them on wood plates placed next to our OPM-MEG system [3]. To drive these coils, we built a low-noise voltage-controlled constant current driver. We generated the control voltage with a computer-controlled commercial signal acquisition card (MEGIN Oy, Finland), which enables both static and dynamic compensation as it continuously receives a low-latency copy of the OPM data. To set up the compensation, we place the OPMs in the MEG measurement volume between the biplanar coils where they measure both the remnant field and specific AC probe fields generated by the coils. Then a linear model is constructed based on the applied coil currents and measured probe fields. Inverting this model and inputting the inverse of the remnant field yields the optimal compensation coil currents. With this automatic approach, we have suppressed the remnant field by at least an order of magnitude in three magnetically shielded rooms, which has enabled high-quality OPM-MEG measurements. References [1] A. Mäkinen et al. Journal of Applied Physics, 128(6), p.063906 (2020). [2] R. Zetter et al. Journal of Applied Physics, 128(6), p.063905 (2020). [3] J. Iivanainen et al., Neuroimage 194, p.244–258 (2019).

P23. MEG hyperscanning meets network science: graph-theoretical exploration of intra- and inter-brain connectivity

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We present data from 10 pairs of participants performing an interactive task, while magnetoencephalography (MEG) was simultaneously recorded from both subjects. In this task, one

person (instructor) provided informative or uninformative instructions to a second person (follower) who moved a piece on a checkerboard. We created binary networks from the source-level weighted-phase-lag-index functional connectivity in the beta-band, both within and across the interacting brains. Our preliminary results showcase the application of graph theoretical metrics, such as degree, clustering coefficient, betweenness centrality, and closeness centrality, to analyze the interaction dynamics between instructors and followers, considering both intra- and inter-brain networks.

P24. The central executive core network of working memory

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Multicomponent working memory (WM) models comprises a short-term storage of sensory information coupled with executive processes. How this could be implemented at the neurophysiological level, is only partially understood. Neuronal oscillations and their inter-areal interactions could provide a clue to this question by serving as a fundamental clocking mechanism for brain activity. We studied if the long-range coupling of neuronal oscillations - phase-synchronization - could implement the central executive core of the visual WM that would enable the memorization of behaviourally relevant visual information. We combined concurrent magneto- and electroencephalography (M/EEG) data with network science approaches to identify the central core of phase-synchronization networks. We show here that alpha-band phase-synchronization differentiates between the memorized features and forms a frontoparietal top-down backbone of WM reflecting the WM contents. Using supervised machine learning, we further show that alpha-band phase-synchronization connectomes yield accurate decoding of VWM contents. Our results establish that alpha-band phase synchronization serves as the core executive network of WM, connecting fronto-parietal and sensory areas accurately and thereby reflecting the contents of memory.

P25. OPTIMIZING MUSIC INTERVENTIONS IN DEMENTIA CARE: Research plan for a PhD thesis

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Research shows that music can support mood, and cognitive and social wellbeing for persons with dementia (PWDs). However, our understanding on how and why music works in the ageing and degenerating brain is limited. Many challenges also remain in the practical implementation of music in dementia. Using cross-sectional and randomized controlled trial (RCT) designs, this study aims to (i) explore music cognition and the nature and preservation of music-induced emotions and memories from healthy ageing to dementia and (ii) determine the applicability and efficacy of a digital music intervention

(DMI) and conventional music therapy (CMT) across the dementia care continuum. The sample comprises 192 PWDs (PWDs with mild-moderate dementia living at home and PWDs with moderate-severe dementia living in care homes; N=96 each) and 30 healthy age-matched control participants (HCs). PWDs in home care and PWDs in care homes are randomized into three groups (DMI, CMT, standard care). The DMI and CMT comprise passive and active engagement with music over 10 weeks (2x60 min sessions/week). The CMT is led by a music therapist. The DMI is implemented using the HILDA content service and does not involve direct therapeutic interaction. To investigate the efficacy of music interventions in dementia, PWDs complete measures of cognitive functioning, mood, and quality of life at three time points across 6 months. To explore neural factors and individual music skills that may mediate the efficacy of music interventions in dementia, PWDs complete structural and functional MRI measurements and a music battery at baseline. The music battery measures music cognition, including music perception, memory, emotions, rhythmic timing, musical movement, singing, and musical background. To compare music cognition and music-evoked emotions and memories across healthy ageing to dementia, HCs also complete the music battery and EEG measurements. Trial number NCT05520268.

P26. Decoding brain activities of literary metaphor comprehension: An event-related potential and EEG spectral analysis

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Novel metaphors in literary texts seem to be more creative and open-ended in meaning than metaphors in nonliterary texts. However, some disagreement still exists on how literary metaphors differ from nonliterary metaphors. Therefore, this study explored the neural mechanisms of literary metaphors from Chinese poems by Event-Related Potentials (ERPs) and Event-Related Spectral Perturbations (ERSPs), as compared with nonliterary conventional metaphors and literal expressions outside literary texts. Forty-eight subjects were recruited to make the semantic relatedness judgment after reading the prime-target pairs in three linguistic conditions. According to the ERPs results, the earliest differences were presented during the time window of P200 component (170–260 ms) in the frontal and central areas, with the amplitude of P200 for literary metaphors more positive than the other two conditions, reflecting the early allocation of attention and the early conscious experience of the experimental stimuli. Meanwhile, significant differences were presented during the time window of N400 effect (430–530 ms), with the waveform of literary metaphors more negative than others in the frontal and central topography of scalp distributions, suggesting more efforts in retrieving conceptual knowledge for literary metaphors. The ERSPs analysis revealed that the frequency bands of delta and theta were both involved in the cognitive process of literary metaphor comprehension, with delta band distributed in the frontal and central scalp and theta band in parietal and occipital electrodes. Increases in the two power bands during different time windows provided extra evidences that the processing of literary metaphors required more attention and effort than nonliterary metaphors and literal expressions in the semantic related tasks, suggesting that the cognitive process of literary metaphors was distinguished by different EEG spectral patterns.

P27. Masked Priming Effects on Metaphor Comprehension in Chinese English Learners: An ERP Study

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Metaphors require the comprehension of meaning that goes beyond the literal interpretation. However, the mechanism behind metaphor processing remains controversial. Masked priming has been utilized in experimental studies on metaphor comprehension to explore how the brain processes metaphorical language and differentiates between literal and metaphorical interpretations. This study aimed to investigate how metaphors are decoded when target words are preceded by masked primes, using event-related brain potentials (ERPs) to examine metaphor processing in Chinese-English learners (EFLs). Participants were asked to judge the sensibility of metaphors presented with various masked primes (metaphorical primes/literal primes/unrelated primes). For Chinese metaphors, a parameter-free cluster permutation analysis of brain responses revealed larger negative amplitudes in the left temporo-occipital areas within the 240-280 ms time window for metaphors with metaphorical primes compared to those with literal primes. Similarly, for English metaphors, significant priming effects were observed within the central brain area within the 400-550 ms time window, characterized by larger LPC positive amplitudes for metaphors with metaphorical primes. These findings demonstrate that metaphorical masked primes facilitate metaphor processing in both native (L1) and second language (L2) learners, likely due to increased automatic activation during early-stage processing.

P28. Hemispheric dominance of metaphor processing for Chinese-English bilinguals: DVF and ERPs evidence

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Figurative language such as metaphor has aroused the interest of researchers for centuries as metaphors are pervasive in our daily life. This study investigated whether Chinese-English speakers processed Chinese and English metaphors, as compared to literal expressions, predominantly at the right or left hemisphere. In addition, the role of familiarity in processing of metaphorical and literal expressions in the first and second language was explored. This study used brain-event-related potentials with a divided-visual-field paradigm. The participants were asked to perform plausibility judgments of familiar and unfamiliar metaphorical and literal sentences for Chinese (L1) and English (L2) languages. The behavioral reaction time results showed that participants needed longer time to process unfamiliar metaphoric sentences than unfamiliar literal sentences. Overall, the reaction times for unfamiliar sentences were longer than those for familiar sentences in both languages. Moreover, it took longer to process English expressions than Chinese in all sentence conditions which shows an L1 advantage. The EEG results obtained using parameter-free cluster permutation statistics showed a significantly larger N400 response for metaphors than literal expressions in Chinese and a slightly larger N400 response for literal expressions than metaphors in English. Both metaphoricity and familiarity had an effect on the brain response patterns for Chinese and English metaphor processing. However, the brain responses were

distributed bilaterally across hemispheres. The results of this study demonstrate a complex hemispheric processing pattern for metaphorical expressions, compared to literal expressions, suggesting, however, no clear evidence for lateralization of metaphor processing. The results also suggest different brain response patterns for metaphor processing between Chinese and English languages.

P29. Snoring was related to self-reported daytime sleepiness and tiredness in young adults performing compulsory conscript service

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Study Objectives: In young adults performing compulsory military service, fatigue and somnolence are common and presumably associated with objective or self-reported sleep deprivation. We aimed to find out whether objective sleep parameters from ambulatory polysomnography could explain their self-reported tiredness and sleepiness and whether habits were associated with sleep parameters or tiredness. Methods: Seventy (67 male, age 18–24 years) participants had their sleep assessed with polysomnography. Their self-reported symptoms and demographic data were obtained from online survey including Epworth Sleepiness Scale, Beck's Depression Inventory, items from Basic Nordic Sleep Questionnaire, Internet Addiction Scale, and lifestyle questions. Results: Snoring (audio recording, percentage of total sleep time) was associated with self-reported sleepiness ($P = .010$) and tiredness ($P = .030$) and snoring seemed to, partially, explain sleepiness ($P = .029$). Twenty-six percent of the conscripts had self-reported sleep deprivation (mismatch between reported need for sleep and reported sleep). Self-reported sleep deprivation was significantly associated with somnolence ($P = .016$) and fatigue ($P = .026$). Smartphone usage, both average time ($P = .022$) and frequency of usage ($P = .0093$) before bedtime, was associated with shorter total sleep time. On average, objective sleep time was rather short (7 hours, 6 minutes), sleep efficiency high (94.9%), proportion of N3 sleep high (27.7%), and sleep latency brief (9 minutes)—suggesting that many of the conscripts might have chronic partial sleep deprivation. Conclusions: Snoring might predispose to tiredness in presumably healthy young adults. Conscripts may have partial sleep deprivation.

P30. Traumatic life events as predictors for depression in men and women: A Finnish twin study

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BACKGROUND: Reasons for higher rate of depression in women compared with men are not fully understood. We examined the prevalence of adulthood traumatic life events (TLEs) and analysed whether the associations of TLEs with depression are independent of gender-based vulnerability or familial confounding. METHODS: 8410 individuals (45% men, mean age 60 years) participated in the fourth survey of the population-based Finnish Twin Cohort in 2011. Depression was assessed using the Center for Epidemiologic Studies Depression (CES-D) scale (cut-off value ≥20). Participants reported their exposure to TLEs (yes/no) during adulthood. Logistic regression adjusted for multiple confounders were used in the individual-based analyses. The effect of shared familial factors was tested using conditional logistic regression in 403 depression discordant twin pairs (34% genetically identical pairs). RESULTS: Rate of depression was 11% in men and 15% in women. Men reported more traffic accidents (men: 12%, women: 7.4%), other serious accidents (12%, 5.8%), and violent crime (3.1%, 2.0%) whereas women reported more sexual abuse (0.7%, 11%), respectively. Serious accidents (Odds Ratio 1.36; 95% Confidence Intervals 1.01, 1.85), physical assault (3.10; 2.45, 3.93), sexual assault (3.49; 2.67, 4.55), and violent crime (3.86; 2.59, 5.73) were associated with depression. Associations, except other serious accidents, remained after adjusting for numerous individual confounders or shared familial factors. Associations between TLEs and depression did not differ by gender. CONCLUSIONS: Women and men differ in their exposure to TLEs but are as vulnerable for depression after an exposure. This should be considered in prevention and treatment of depression.

P31. Spatially intermixed color distributions are segmented by hue, not by color category

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Color can be used to group similar objects, but can the visual system segment scenes according to arbitrary color distributions? We examined whether observers can extract the ensemble mean hue from a target hue distribution among distractors, and whether a category boundary between target and distractor hues facilitates segmentation. Ensembles consisted of 18 uniformly colored circles with hues drawn from uniform distributions on a hue circle in CIELUV color space. Circles (0.5° of visual angle) were located randomly in a 6-by-6 invisible grid with 1° element separation. The test stimulus contained the target ensemble in the baseline condition, and the distractor and target ensembles in the experimental conditions. The comparison stimulus was one ensemble with mean hue varying around the target mean hue. In Experiment 1, mean target hue was red or green, and distractor mean hue was shifted 180° or 60° from target mean. In Experiment 2, mean target hue was on either side of the green-blue color boundary, and distractor mean shifted 45° from target mean within the same category or across the category boundary. The test and comparison stimuli were presented in two 500ms intervals, separated by 500ms. Observers responded whether the second ensemble appeared on average bluer/purpler or yellower/greener than the first ensemble, ignoring the distractor ensemble. Psychometric functions were fit to the proportion of responses to estimate perceived target hue and discriminability. Observers could selectively judge the target ensemble mean hue, but discrimination thresholds were higher the closer the distractor mean was to the target mean. Perceived target ensemble mean hue was biased towards distractor hues, and bias magnitude varied between experimental conditions. Color category boundary between target and distractor hues did not affect discriminability or bias. To conclude, observers can segment spatial color distributions within and across color category boundaries.

P32. Tempting tastes in focus: forming a picture set of high-fat/high-carbohydrate foods for the Finnish population

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Recent evidence suggests that the dietary composition (high in fat, refined sugar, or both) of modern food items can alter brain reward processes, which contribute to the prevalence of obesity and metabolic disease. Food images are a good tool to investigate diet effects on eating behaviour. However, there is a lack of representative high-quality food images and high specificity makes studies difficult to replicate. To investigate these dietary effects in a controlled setting, stimuli relevant to the studied population are required. Therefore, we are creating a novel food picture set for the Finnish population. We photographed 72 food items that are commonly purchased and consumed in Finland and based on the package information, classified them into one of three macronutrient categories: (1) high in carbohydrates (C), (2) high in fat (F), or (3) high in C and F, called combo. 36 participants rated the food items' liking, familiarity, frequency of consumption, expected satiety, healthiness, energy content, and energy density. Our goal is to minimize differences between the categories on familiarity. Thus ensuring our picture set is appropriate for studying eating behaviour in Finland. Using Bayesian ANOVA, we provide complete information on food characteristics, visual properties and participant ratings. We found strong evidence of differences between the macronutrient groups in protein (BF= 147417.9±0%), fibre (BF= 25.858±0.01%) and salt (BF= 2361.440±0%). Moreover, our data showed strong evidence that our items differ in liking (BF= 13.205±0.01%) and moderate evidence of no differences in familiarity (BF= 0.344±0.03%). In this study, we created a database featuring food images that accurately reflect the current obesogenic environment in our location (Finland). We anticipate that our picture set will support researchers in Finland to conduct experiments on food choice and eating behaviour while facilitating replicability and comparability of studies in the field.

P33. Critical-like bistable dynamics characterize Alzheimer's disease progression

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Recent studies support the central role of synaptic loss leading to excitation/inhibition (E/I) imbalance, which prompts subclinical epileptiform activity as the primary initiator of Alzheimer's disease (AD), and consequently neural network dysfunction. The classic brain criticality hypothesis posits that

neuronal systems operate in the vicinity of continuous phase transition, regulated by E/I balance. This provides the brain with optimal dynamic range, which is essential to healthy cognition and behaviour. However, due to positive feedback —a slow parameter in addition to E/I— neurons show bistable activity, demonstrating discontinuous phase transition. It is suggested that a moderate and elevated degree of bistability in ongoing neuronal oscillations were predictive of cognitive performance in healthy adults and neuropathology in epilepsy and geriatric subjects, respectively. Since there is growing evidence of presence of subclinical epileptiform activity in patients of AD that can hasten cognitive decline, we aim to characterize such events with bistability analysis and provide mechanistic understanding of disease progression. We analysed resting-state MEG data recorded from 85 preclinical (SCD: Subjective Cognitive Decline), 142 prodromal (MCI: Mild Cognitive Impairment), 14 AD patients, and 116 healthy controls (HC). MNE estimated sources were collapsed into 400 parcels with a fidelity-optimized operator. Parcel broadband data were then filtered with 32 wavelets within a range of 2–90 Hz and bistability (BiS) indices were estimated. We found aberrant BiS for SCD, MCI and AD compared to HC over the spectrum of 7–40 Hz. Importantly, BiS differentiated early disease stages and had frequency specific between-cohort differences. The results suggest BiS already alters at the early stages of AD, progressively alters with disease progression, and can potentially be utilized as a biomarker for AD diagnosis and prognosis.

P34. Oscillatory mechanisms of serial and concurrent visual working memory

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Visual working memory (VWM) is the ability to retain a limited amount of visual information for a brief period of time. VWM has been investigated using both delayed match-to-sample (DSM) tasks where visual objects are presented concurrently and Sternberg-like memory tasks where visual objects are presented serially. These tasks have revealed VWM capacity of ~3 +/- 1 and 7 +/-2 concurrent objects, respectively. The present study aims to investigate the differences of oscillatory mechanisms between concurrent multi-item VWM in a DMS task and serial VWM using concurrent magneto- (MEG) and electroencephalography (EEG).

P35. Oscillatory mechanisms of bilateral visual working memory

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Visual working memory (VWM) is the ability to remember, manipulate, and reproduce visual stimuli even in their physical absence. VWM has a limited capacity, which is larger if stimuli are presented bilaterally vs unilaterally. However, the neuronal mechanism underlying this bilateral field advantage is not known. VWM capacity is predicted by de-/synchronization of local oscillation and inter-areal

synchronization during VWM. In this study, we asked whether de-/synchronization of local oscillation and/ or their inter-areal synchronization across brain areas could explain the bilateral field advantage and larger memory capacity for bilaterally presented stimuli. We recorded brain activity with high-density (HD)-electroencephalography (EEG) while subjects (N=26, 14 males) performed a delayed match-to-sample VWM task with uni- and bilateral visual stimuli. VWM capacity was larger for bilateral than unilateral presentation of visual stimuli. Bilateral VWM was associated with a stronger decrease in alpha-band amplitudes and concurrent stronger load-dependent increase in high alpha-bands amplitude and inter-areal synchronization. Both alpha amplitudes and synchrony correlated well with hit rates and thus seemed to be predictive of bilateral VWM performance. These results demonstrate the electrophysiological basis of bilateral VWM capacity and performance differences.