Investigation of the neuronal pathophysiology of tick-borne encephalitis virus with infant rat models

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Rapid spread of infectious diseases of zoonotic origin is a major concern. Arthropod-borne flaviviruses, as tick-borne encephalitis virus (TBEV), represent a major threat to European countries. Currently, the exact pathological mechanisms driving acute neurological manifestations in patients affected by a neurotropic flavivirus infections remain poorly understood. Our hypothesis is that the extent of damage and the sequelae caused by neurotropic flavivirus infections are influenced by their ability to invade the central nervous system, to replicate with high efficiency in various cell types, and/or to induce high inflammation (immune response) and damages. Different strains of the European subtype of TBEV, mostly isolated from ticks in Switzerland, will be compared in terms of neuro-invasiveness, neurovirulence, and mechanisms mediating neuronal injury. *Ex vivo* (hippocampal and cerebellar organotypic cultures) and *in vivo* (infant Wistar rats) models will be exposed to the virus to investigate neurovirulence and neuro-invasiveness. The level of viral replication will be assessed using rt-qPCR and $TCID_{50}$ on Vero cells, while the cellular tropism will be determined using immunofluorescence. Furthermore, RNA sequencing and other biochemical approaches will be used to determine the host inflammatory and immune responses. Finally, once established, these models will be used to test different antiviral compounds to determine if they can improve the outcome of the neuronal disease.

Stability of hypothalamic neural population activity during sleep states

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Sleep is a primary and essential biological need for most animals. Many brain regions and neural circuits have been implicated in the regulation of sleep and wakefulness, in particular, the lateral hypothalamic area (LH) is central to the orchestration of sleep–wake states, feeding, energy balance, aversion and goal oriented behaviour. This suggested that some of these cells may share both sleep and metabolic functions. In this study, we longitudinally image the activity of VGat and VGlut2 neurons in freely behaving mice over a week using in vivo calcium imaging, and compute a categorization of their activity across wake, REM and non-REM states and across days. We found that part of the cells remained within the same cluster (wake, NREMS or REMS active), however, a significant portion of these 'recluster' into different categories at different times of the day, and over multiple days. Finally, we described the stability of these clusters upon sleep recovery (sleep deprivation). Our findings shed light on the dynamics and plasticity of several neuronal populations in different sleep-wake states and help to better understand multitasking functions of LH circuits.

Neuropathophysiological mechanisms in functional neurological disorders (FND): a study on persistent postural-perceptual dizziness (PPPD) - Study Design

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Background: Patients with functional neurological disorders (FND) experience neurological symptoms without an underlying organic cause. Several subtypes, such as functional motor disorders, functional cognitive disorders or functional seizures have been delineated. Subtypes can be distinguished, but they share similarities in aetiology and pathophysiology. Recently, a new subtype of FND was added, namely Persistent postural perceptual dizziness (PPPD) which is characterized by alternating symptoms of dizziness, unsteadiness, or non-spinning vertigo. Until now, relatively few is known about the neuropathophysiology of PPPD.

Objective: This study aims to gain further knowledge on PPPD by investigating why patients develop PPPD and how symptoms emerge.

Methods: Thirty patient with PPPD, 30 organic control patients and 30 healthy control subjects will participate in study visits 1 and 2, which will consist of questionnaires, blood and saliva samples, and structural and functional MRI. The PPPD patients group will repeat the examination 8 months later at study visit 3.

Planned analysis: To answer why PPPD emerges, clinical data on stressful life events, stress markers and genetic markers will be compared between patients with PPPD, organic control patients and healthy control subjects. Addressing how symptoms occur, analysis on structural and functional characteristic, such as brain functional connectivity, will be conducted and compared between patients with PPPP, organic control patients and healthy control subjects.

Relevance: Findings from this study will contribute to a better knowledge of PPPD and therefore, might improve the process of diagnosis and treatment options.

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Cross-modal effects after stroke – the influence of sensory stimulation on visual neglect: a proof-of-concept study

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Spatial neglect after right-hemispheric stroke is characterized by the failure to perceive stimuli presented in the left, contralesional hemispace. In spatial neglect, the visual modality is typically more often and more severely impaired compared to the auditory modality. This dissociation may lead to beneficial cross-modal effects, whereby auditory stimuli may improve visual neglect. Indeed, a new auditory spatial cueing stimulation with music moving dynamically from the right to the left space has been shown to improve visual neglect. The aim of this proof-of-concept study was to compare the effects of auditory spatial cueing with visual spatial cueing (an established therapeutical approach in neglect therapy) and to explore whether a combination of auditory + visual spatial cueing would lead to additive effects. Our results showed that unimodal auditory spatial cueing improved neglect to a significantly higher degree than unimodal visual spatial cueing. Multimodal spatial cueing improved neglect, yet there is no additional therapeutical gain in combining auditory + visual spatial cueing. In neurorehabilitation, the implementation of either auditory or visual spatial cueing seems therefore reasonable.

Circadian timing of limbic seizures in the epileptic mouse

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Background: In epilepsy, seizures often recur with striking regularity at certain hours of the day in the human and mouse epileptic brain. Fundamentally, this observed preferential timing may result from the active-rest history (or sleep-wake, so-called process S) and/or from the circadian rhythm intrinsic to any neuron (so-called process C). The aim of this study is to disentangle the individual contributions of process S and C to the timing of seizures in the Kainic Acid (KA) mouse model of temporal lobe epilepsy.

Methods: We recorded spontaneous seizures in epileptic mice (n=9) over months using 16 depth-electrodes implanted in the limbic circuit. These animals were kept in a 12:12 light-dark cycling environment (LD), before subjecting them to different experimental schedules: 1) constant dim red light (DD), 2) constant light (LL), 3) 10:10 light-dark cycling (T20). We identified the underlying circadian and active-rest cycle based on core body temperature (CBT) and actimetry, respectively, and extracted the preferred phase at which seizures occurred.

Results: We observed a circadian clustering of seizures between the peak and the falling phase of 24-hour activity in LD (PLV= 0.29+/-0.18). While the circadian clustering persisted at the same phase during DD (PLV= 0.27+/-0.01) it was attenuated in LL (PLV= 0.16+/-0.07), when the strength of the underlying circadian cycle was also weakened. Under T20, we observed a periodic uncoupling of the active rest cycle and CBT cycle (about every third day). The clustering of seizures was higher during the period when both cycles were aligned (PLV= 0.54+/-0.14) and lower when they were misaligned (PLV= 0.32+/-0.13).

Conclusions: The temporal clustering of seizures depends on the strength and alignment of Process S and Process C, which may help guide chronotherapeutic interventions in the future.

Neural representation of future outcomes is affected by decision context

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Introduction: In our daily lives we make numerous decisions, such as whether to carry an umbrella. The possible outcomes of decisions are retrieved and represented in the brain before the decision itself is made (Castegnetti et al., 2020; Shadlen et al., 2016). However, most studies treat decisions as detached from their context, which is not realistic. For example, the decision to carry an umbrella is affected by the season and chance of rain. In fact, context modifies value computation, allowing flexible adjustments of behaviour (Castegnetti et al., 2021). Although there is evidence that decision-making is a dynamic process which can be altered by context, how context is neurally integrated in decision deliberation is still unknown. We hypothesized that the likely outcome of decisions is retrieved and represented neurally before a choice is made and that integration of context strengthens retrieval of likely outcome.

Methods: We designed a decision-making task in which participants were presented with object and context pairs (gardening tools and fictional seasons) and had to make a decision on their most likely outcome (gardening outcome). In the majority of decisions, context determined the likely outcome of a given object (contextdependent), while in a control condition outcome was independent of context (context-free). We recorded high-density electroencephalography (EEG) from 26 healthy participants.

Logistic regression classifiers were trained on EEG responses to decode the identity of three possible outcomes, presented before the decision-making task. Outcome retrieval was quantified by the reconstructed probabilities of the trained outcome classifiers, applied on EEG activity during deliberation. As we did not expect outcome retrieval to be time-locked to a specific event, we tested whether the power spectral density of reconstructed probabilities was different from chance, and we computed their temporal structure via the autocorrelation function (Castegnetti et al., 2020). As context appeared at a given point in time, the effect of context was evaluated via time-locked analysis of reconstructed probabilities. Chance was computed empirically by training classifiers with 100 random permutations.

Results: Behaviourally, participants were significantly more accurate in choosing the correct outcome for a given object-season pair in context-free than context-dependent decisions ($p<0.05$). The classifiers trained to discriminate the identity of the three possible outcomes performed significantly above chance ($p_{FDR}<0.05$) and were then applied to reconstruct outcome representations during decision deliberation.

We found a significantly stronger than chance power in the representation of reconstructed outcomes during deliberation, between 3 and 19 Hz ($p_{FDR}<0.05$). The autocorrelation of the

reconstructed outcome representations significantly differed from chance for time lags between 31 and 168ms (p_{FDR}<0.05). These findings support our hypothesis that the neural representations of likely outcomes are retrieved during deliberation, before a choice is made and before the outcome is experienced.

Upon presentation of context, the most likely outcome was more strongly represented for context dependent decisions compared to context-free ones, starting at 230ms after context presentation. In the control context-free condition, the representation of likely outcomes was not affected by the presentation of context.

Conclusions: We showed that the neural representation of anticipated outcomes is retrieved with significantly higher than chance power as early as 5s before a choice is made. In cases when context is affecting a decision, integration of context into outcome retrieval takes place as early as 230ms after context is presented. Our results suggest that representation of future outcomes and context are a dynamic and integral part of decision making.

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High-Density surface EMG based evaluation of post-stroke rehabilitation progress.

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Stroke affects more than 100/100,000 of the world population per year. Motor deficit is the most common impairment in stroke patients.Early rehabilitation is considered critical in stroke treatment. For instance, most patients present 70% of motor recovery regardless of the type of therapeutic intervention. However, although some patients with severe initial motor impairment have proportional recovery, some others do not. To achieve a greater proportion of motor rehabilitation and to improve functional outcomes, rehabilitation therapy should implement personalized strategies that adapt according to the evolution of motor behavior. A deeper knowledge on the mechanisms of motor recovery via the assessment of the neuromuscular system could help as a guidance for more personalized treatment.

Effects of concurrent phase-locked tACS-iTBS on neural plasticity in the prefrontal cortex

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Repetitive transcranial magnetic stimulation (rTMS) provides means to alter cortical excitability in an excitatory or inhibitory manner. Theta burst stimulation (TBS) seeks to improve the methodology of rTMS by applying TMS pulses in a way that mimics endogenous theta rhythms, resulting in a much shorter application time compared to standard rTMS protocols. The problem remains that there is high interindividual variability in response to these protocols.

Possible causes of these variabilities could be anatomical variations but also the phase of the ongoing oscillatory activity in which TBS pulses are applied. Previous studies have shown that the extent of the neuronal response to TMS is dependent on this phase: pulses applied at crests elicit greater potentials compared to those applied at throughs. In the case of TBS, pulses are randomly applied and might coincide with throughs of the natural oscillatory activity and thus not able to reach a certain threshold of activation in the cells to induce long-term potentiation (LTP).

Transcranial alternating current stimulation (tACS) can shape the state of cortical excitability in a phase-dependent manner. Applying tACS at theta frequency could be utilized as a sort of priming instrument for TBS. While cortical excitability is increased at crests of the tACSinduced current, applying the TBS triplet pulses at the crests of tACS has the potential to produce larger neuronal responses and thus increase the likelihood of LTP. In our ongoing randomized sham-controlled study, we seek to further increase the cortical excitability of the prefrontal cortex by pairing tACS with a concurrent phase-locked iTBS protocol.

Twenty-six healthy participants will undergo two intermittent TBS (iTBS) sessions, once paired with sham-tACS and once with active tACS in a cross-over design. The effects of the phase-locked concurrent stimulation will be assessed by comparing TMS-induced activity in the EEG before and after the simulation as well as between the two sessions as a measure of cortical excitability. We hypothesize that it will vary significantly between pre- and post-iTBS as well as between sham- and active-tACS sessions.

Retrosplenial Cortex Activity: a Hub in a Paradoxical Sleep Network?

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Rapid eye movement (REM, also called paradoxical) sleep correlates with enhanced cellular activity of region-specific thalamo-cortical circuit and subcortical structures including the hippocampus, midbrain or hypothalamus. This REM sleep specific neuronal activity is hypothesized to promote structural plasticity and provide a window for the consolidation of contextual and emotional memories previously acquired during wakefulness, yet the underlying mechanism remains unclear. Amongst the cortical structures, the activity of neurons located in the retrosplenial cortex (RSC) is increased during REM sleep. Yet, cortical single cell-to-whole brain circuit connections and its role in REM sleep function remains unknown. Here we characterized the activity of RSC microcircuit across the sleep-wake cycle using simultaneous 2-photon calcium imaging and electrophysiological recordings in spontaneously head-restrained sleeping mice. We observed a REM sleep-specific reduction of pyramidal cell somatic activity concomitant to the activation of the interneurons expressing either parvalbumin, somatostatin or vasoactive intestinal peptide. Collectively, these observations suggested a region-specific regulation of excitatory/inhibitory balance in RSC during REM sleep that may contribute to information integration, memory consolidation and ultimately behavioural optimization.

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Topographic Mapping of EEG and Evoked Potentials in Pre-Reflective and Reflective Self-Experience – Role of Default Mode Network and Cortical Midline Structures

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Introduction. The notion of selfhood is fundamental in human consciousness and has been divided into two main components, the minimal or pre-reflective (i.e., first-person) perspective and the narrative or reflective (i.e., third-person) perspective. So far, evidence on the neural correlates of these components is scarce, despite their importance in physiological conditions, like dreams and out-of-body experiences, and in psychopathology with self-disorders. With our study, we investigated their event-related potentials (ERPs) correlates with a lexical task in healthy volunteers.

Methods. 30 individuals (22F, 8M; mean age 25.2 years) performed a lexical task where they expressed trait judgments on the self or on a close other to elicit pre-reflective and reflective self-states during a 64-channel EEG recording. With the data, we performed both ERP analysis with the topographic analysis of variance (TANOVA) method and source localization with standardized low-resolution brain electromagnetic tomography (sLORETA).

Results. We identified a window of difference between topographies of pre-reflective and reflective self-experience at 254-310 ms post-stimulus-onset. The sources contributing to the difference were located, for the self-reference, in the right frontal, parietal, and temporal areas, and, for the other-reference, in the left frontal, cingulate, and parietal areas, and in the right temporal and cingulate areas.

Conclusions. Our results confirm different neural correlates in pre-reflective and reflective self-experience. The source analysis pointed at a right laterality in pre-reflective and to a more distributed involvement in reflective states. The networks engaged include cortical midline structures (CMS) and default mode network (DMN), which have an important role in self-related processing. In addition, the bottom-up ventral attention network is involved in pre-reflective self-experience and the top-down dorsal attention network in reflective self-experience.

Assessing Speech Processing During a Functional Near-Infrared Spectroscopy Task in Normal Hearing Listeners and Cochlear Implant Users

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Aims

Hearing outcomes after cochlear implantation (CI) vary considerably. There is evidence that plastic brain changes caused by hearing loss, correlate to different hearing outcomes. Our aim is to measure speech processing related brain activation patterns in normal hearing (NH) and CI-wearing adults. These patterns can delineate plastic brain changes and its role after surgery.

Materials and Methods

We recruited 26 NH and 14 CI participants (postlingually deafened, Freiburg test > 75%). While they performed an audiovisual speech processing task, we measured their brain activity with functional near infrared spectroscopy (fNIRS). During the stimulation period, participants listened to 13 seconds long video-recordings of the Oldenburg Sentence Test (OLSA). The stimulations were presented in 4 different modalities: speech-in-quiet, speech-in-noise, visual speech (i.e., lip reading) or audiovisual speech. Each stimulation type was repeated 10 times in a counter-balanced block design.

Results

During the stimulation periods, we measured different activation patterns in the temporal and occipital regions in NH and CI subjects.

Following speech-in-quiet stimulation, we measured cortical activation the temporal regions of both groups, and it was slightly stronger in NH subjects. During visual speech, we measured weak temporal activation in both groups, which was slightly stronger in CI subjects. Interestingly, occipital activation during visual speech was present only in NH and not in CI subjects.

Conclusion

The differences in brain activation between CI and NH participants could be explained by brain plasticity. Further data is needed to confirm the results (data collection is ongoing).

The role of Oxytocin and Interoception in Functional Neurological Disorder (FND)

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The mechanisms behind Functional Neurological Disorder (FND) is still unclear. This research project aims to approach FND from a Bayesian Brain perspective by focusing on the interoceptive modality. In specific, the hypothesized dysfunctional precision weighting of interoceptive signals will be tested, while considering the specific effect of the hormone Oxyotcin (OT) in this regard. For that, 42 FND patients and 42 healthy controls will be recruited to complete interoceptive tasks on both the cardiovascular and the respiratory domain, while also measuring electrophysiological changes associated with the heartbeat. Further, saliva and blood samples will serve to measure peripheral OT and to analyze OT-associated (epi-)genetics, which finally allows to correlate the OT-system with interoception and symptoms of FND.