Group 1 - Sleep

Keywords: Thalamus, sleep, stroke, cognition

Thalamic stroke effects on sleep-wake regulation and cognition The

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The structure and dynamics of neural systems regulating arousal and cognition remain partially understood. An increased knowledge about this neuronal network, and its central thalamic hub, might lead to insights for treating neurological and consciousness' disorders. Thalamic strokes usually lead to these dysfunctions that are debilitating and, in many cases, long lasting. Among thalamic infarcts, the paramedian stroke accounts for about 35% of the cases, and its symptomatology includes hypersomnia accompanied by altered non-REM (NREM) sleep, and cognitive impairments. Hermann et al. (2008) observed that in patients with paramedian stroke hypersomnia was related to poor clinical outcome, which in turn was associated with persistent deficits in attention. This observation led to the hypothesis that sleep and cognition are related functions, possibly sharing a common neuronal network modulating them both. The present study aimed to characterize the sleep- and cognitive-related phenotypes resulting from lesions of different thalamic nuclei. Here, we used a model of targeted mini-stroke obtained via induction of photothrombotic lesions in the CMT territory (Braeuninger & Kleinschnitz, 2009). In parallel, EEG/EMG recordings were used to characterize the evolution of sleep parameters and sleep oscillations over the entire period between pre- and post-stroke induction, in both lesioned and sham animals. Behavioral changes were measured via the open field test (OFT), forced alternation task in the Y-maze (YM) and pain sensitivity test assessing the foot-shocks sensory threshold, in both groups of animals.

Our preliminary results show that CMT-stroke animals presented: 1) altered sleep architecture and oscillations; 2) reduced exploration levels in the OFT and significantly increased number of trial errors with reduced latency-to-reward in the forced alternation task, and lower pain sensitivity threshold, in comparison to the sham group. Overall, these first results are consistent with both clinical and recent animal studies indicating a role of the medial thalamus in orchestrating sleep and wake states (Gent, Bandarabadi, Herrera, & Adamantidis, 2018; Mátyás et al., 2018). Moreover, high perseveration in the working memory task is consistent with previous findings suggesting a role of the CMT in encoding for prediction error and associative learning (Matsumoto et al., 2001, 2005; Yamanaka et al., 2017).

Abstracts for selected Symposia

Keywords: pain, sleep, LFP, thalamo-cortical, somatosensory

Touch and Pain Processing during Sleep

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During sleep, the thalamic nuclei that gate information to the cortex highly increase the sensory threshold. Consequently, the amount of information reaching cortical areas is severely reduced. Nonetheless, both visual and auditory signals have been shown to be able to reach the cortex and be processed during sleep. In fact, thalamo-cortical oscillations during sleep contribute to the processing and learning of sensory inputs. Furthermore, it has been hypothesized that sleep optimizes memory consolidation of the sensory experience. However, it remains to be elucidated how the thalamo-cortical network processes painful stimuli during sleep.

Here we investigate the processing of touch and acute painful stimuli during sleep. We use multi-site implantations to simultaneously record the electrophysiological response to pain and touch in different thalamo-cortical regions. Preliminary results indicate that, as visual and auditory stimuli, painful stimuli can also be relayed to the cortex and be processed during sleep. Understanding the thalamo-cortical circuits involved in the gating of painful stimuli during different arousal states will allow us to tackle the underlying cause of chronic pain, a condition which still does not have an effective treatment.

Modulation of brain circuits for sensory processing during sleep states

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Sleep is associated with a sensory disconnection from the environment, thought to be mediated by a thalamic gating of sensory-motor processing, however, to what extent consciousness is deactivated and how sensory information is processed during sleep remains unclear. The thalamus has been proposed as a possible hub for processing sensory inputs during sleep through what is classically described as sensory gating during sleep. Here, we investigated the thalamo-cortical circuit dynamics across sleep states (wakefulness, NREM and REM) upon auditory stimulation. In particular, we compared single-unit activity and LFP responses from freely-moving wild-type mice by implanting electrodes simultaneously in the primary auditory cortex (Au1), the central medial thalamus (CMT), the medial geniculate (MG) and the hippocampus (HP). Average LFP responses in primary auditory cortex and hippocampus had similar waveforms across wakefulness and NREM sleep, characterized by a first negative peak following stimulus onset and a sequent positive peak higher in primary auditory cortex compared to the hippocampus. However, the amplitude of the negative and positive peak was higher in NREM compared to wakefulness. Interestingly, we found a similar response in both the targeted thalamic nuclei, characterized by two negative peaks with the highest amplitude during NREM. Evoked single unit activity (SUA) from the same channels revealed the nature of the LFP peaks, with the negative peak characterized by high firing rate (UP state), and the positive one with low firing rate (DOWN sate). Moreover, since the CMT has been already known for its contributions to cortical UP and DOWN states and arousal, we investigated its role in sensory-evoked awaking probability, finding that its activity promotes arousal. Furthermore, we also performed auditory-cued fear conditioning followed by re-exposure to the sound cues during the subsequent sleep, in order to investigate possible alteration of acoustic memories fear-related. These results suggest that sensory disconnection during sleep occurs at a stage later than primary sensory areas with a central role of the thalamus, and a particular involvement of NREM sleep. Further studies are needed to unravel the neural circuit supporting auditory processing during sleep and in what way sleep might influence the processing of sensory stimuli.

Keywords: sleep, hypnagogic states, hypnagogic hallucinations, emotions, conscious states

Hypnagogic states are quite common: Evidence from a Swiss population

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The hypnagogic state refers to experiences in different modalities, which sometimes occur in the transitional phase between wakefulness and sleep. While the hypnagogic state has been a topic of interest for over a century, its prevalence is still unclear. Moreover, the emotional nature of those experiences remains equivocal, from frightening to emotionally flat. The goal of this project was to investigate these questions in a healthy swiss population. In an ongoing web survey with currently 480 respondents, we assessed different states of consciousness, as well as their modalities. Further, we asked respondents about characteristics of their hypnagogic experiences and assessed cognitive, personality and behavioural influential factors. The preliminary results show that hypnagogic states occurred quite frequently, in 76.5% of respondents. The most frequent hypnagogic experiences were kinaesthetic (92%), visual (59%) and auditory (35%). Most often they occurred at sleep onset (85%), less often at sleep offset (26%) and rarely during the day (7%). Hypnagogic states were described as significantly less irritating than dreams, but similar in their emotional quality. Higher scores in *unusual perception* were associated with a higher occurrence of hypnagogic states, while higher scores in *magical thinking* and *eccentric behaviour* were associated with more pleasant hypnagogic experiences. In addition, higher anxiety was associated with more irritating hypnagogic experiences. Our findings indicate that hypnagogic states are very common and similar to dreams in their emotional quality.

Abstracts for selected Symposia
Keywords: Sleep Disordered Breathing, Stroke

Predicting sleep disordered breathing acutely after stroke: comparing eight sleep questionnaires and a logistic regression model

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Introduction

Sleep disordered breathing (SDB) is common in stroke patients and negatively affects its outcome. How to diagnose SDB in this setting is a matter of debate. The objective of this study was 1) to evaluate the performance of seven sleep apnoea-screening questionnaires to predict SDB in acute stroke patients and 2) to assess the additional predictive power of stroke specific factors.

Methods

Within a prospective multi-centre cohort of acute stroke patients, we studied 395 individuals who underwent early limited channel cardiorespiratory testing. Several SDB pre-screening questionnaires were assessed (the Berlin Questionnaire was filled in by the patients; STOP-BANG, NoSAS, SACS, NoApnea, SOS and SLEEP-IN scores were derived from available data). Sensitivity, specificity, positive predictive values, negative predictive values and the area under the receiver operating characteristics (ROC) curve (AUC) were calculated for different SDB severities, determined by AHI 15 and 30/h. We studied the impact of stroke specific factors on SDB prediction with univariate and multivariate logistic regression analysis. Significance was determined at $p < 0.05$.

Results

The pre-screening questionnaires for SDB show a poor to fair performance in our study (AUC-range 0.579-0.692). The two stroke specific questionnaires (SOS: AUC 0.579, and SLEEP-IN: AUC 0.638) did not outperform the any of the other tests. Logistic regression analysis revealed a number of stroke specific factors associated with SDB, such as cardio-embolic stroke etiology (for AHI >15/h, $p = 0.003$) and NIHSS at discharge (for AHI >30/h, $p=0.037$), besides the known SDB predictors age, BMI and witnessed apnoea's. The multivariate logistic regression model showed a significantly better predictive power for AHI ≥ 15/h (NPV 0.89, PPV 0.47, sensitivity 0.84, specificity 0.57, AUC 0.76) than most of the validated tests, except for the STOP-BANG test ($D = 1.6002$, $df = 612.72$, p-value = 0.1101) and the SACS score ($D = 1.9298$, $df = 335.83$, p-value = 0.05448).

Conclusion

Neither the pre-screening questionnaires nor the multivariate logistic regression model are sufficiently powerful to diagnose SBD in acute stroke patients. Instead, these questionnaires can help to preselect high-risk patients for early testing with limited channel sleep studies for early diagnosis and treatment of SDB.

Abstracts for selected Symposia
Keywords: sleep, perceptual learning, generalization, transfer

Generalization of visual perceptual learning: The role of sleep

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Sleep promotes visual perceptual learning (VPL) and thus optimizes performance of the sensory system. Although VPL is typically specific to the trained task, transfer to untrained stimuli or tasks has been shown. Such generalization may as well benefit from sleep and could provide additional insight into structural and functional mechanisms underlying VPL. We investigate transfer-effects from a trained stimulus to four different untrained stimuli using an orientation discrimination learning task. Human participants are trained in an adaptive procedure to discriminate the orientation of Gabor stimuli (ranging from 30° - 60° with respect to a reference line). Transfer is tested using the identical task and procedure in four different stimuli. Discrimination thresholds are measured before, between and after two 12h intervals, and we train subjects two times within the first 12 hours. In one 12h interval participants sleep a full night at home wearing a sleep tracker. In the other interval subjects go about their daily business. Half of participants start in the morning, the other half in the evening. We expect a larger improvement for transfer stimuli resulting from the interval with sleep. In line with expectations, first results show improved discrimination performance for pooled transfer stimuli restricted to the interval containing sleep. Moreover, data of yet incomplete sample size point to an effect of sleep for two of the four transfer stimuli if the first training was followed by sleep.

Keywords: Thalamic strokes, Spindles, Sleep Consolidation

Differential Spindle Expression Dependent Upon Thalamic Nuclei Lesioned By Stroke

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Introduction

Although ischemic strokes encompassing the thalamus may be small, they have the potential for significant clinical consequences. Thalamic strokes may alter sleep consolidation. Clinical outcomes are usually considered in line with the impacted vascular territory. We investigated the effects of lesioned thalamic sub-structures on electroencephalographic (EEG) spindles, non-rapid eye movement (NREM) sleep markers, known to be global and local phenomena.

Methods

All-night high-density EEG was recorded in 37 patients; from which 15 (48-80y.o, 12 males) presented with thalamic infarcts, determined by diffusion-weighted-images. The extent of the thalamic lesion was quantified by a normalized atlas-based parcellation approach. From this subset, individual spindles (n=24880) were detected from NREM2-3 epochs of 15 acute nights (2.06±1.44 days) after stroke. One subject was excluded due to low recording quality.

Results

As a group, the sleep architecture showed a high proportion of NREM1 (mean 25.08±10.69%). A state transition analysis demonstrated that 46% of transitions from NREM2 were to NREM1, while 15% were to NREM3. Individual spindle power, as well as spindle globality (% of channels involved in a spindle) were significantly reduced if the lesion encompassed either the intralaminar (IL), the mediodorsal (MD) (two-sample t-tests, $p<0.001$). The reduction in power of spindles detected frontally was stronger when left (LMM E=-0.07, p-value=$1.61e^{-05}$) or bilateral (LMM E=-0.33, p-value=$6.93e^{-23}$) IL/MD were lesioned. LMM further confirmed the preponderant role of distinct thalamic nuclei in the expression of individual spindles. Moreover, the impact was significantly different on frontal than on parietal spindles (dependent variables: power, globality; predictors: spindle types interacting with the damaged structure percentage [continuous variable]; random effect: subjects).

Conclusion

These preliminary results suggest a differential effect on individual spindle expression depending on the specific thalamic nuclei affected. Local spindles also appeared to be differentially affected. These data suggest a quantification of affected thalamic nuclei may be key in understanding the impact on spindle characteristics during sleep. While the environment participates in the sleep fragmentation, specific lesions resulting in lower spindle propagation suggest intrinsic loss of thalamic connectivity leading to difficulties in consolidating sleep. Further investigations will evaluate if potential differential homeostatic processes through the night are also observed.

Keywords: Functional neurological disorders, Mindfulness Based Stress Reduction (MBSR), Stress

The Effect of a Mindfulness-Based Stress Reduction Program in FND – Design and Preliminary Results

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Background: Functional neurological disorder (FND) is a disorder in which patients present with a variety of neurological symptoms involving the motor system (e.g., weakness, tremor, seizures) and the sensory system (e.g., numbness, pain). However, in contrast to known disorders associated to those symptoms (e.g., stroke, epilepsy, movement disorders), no underlying organic brain damage can be identified. The pathogenesis of FND is partially unknown, but some studies suggested a role of stress and abnormal emotional awareness/regulation as predisposing factors. Detailed understanding of the interaction between stress and FND is however still missing.

Objective: The aim of this study is to investigate the effect of a mindfulness-based stress reduction (MBSR) program on stress and emotional awareness in FND.

Methods: In a longitudinal randomized controlled trial, 12 FND patients were recruited. During an 8-week interventional phase, 6 patients participated in a standardized MBSR program (active group), while another 6 patients followed their therapy as usual (control group). Before and after the interventional phase, both groups were tested for quality of life, perceived stress, symptom severity, interoceptive awareness and abilities in mindful cognition using self-reported questionnaires.

Results: At baseline, no significant differences were detected between the two groups. Comparing post-intervention to pre-intervention, patients participating in the MBSR program reported higher emotional awareness and enhanced abilities in mindful observing of internal and external phenomena compared to the control group. Furthermore, physical health improved over time in the active group compared to the control group. No changes in perceived stress or symptom severity was reported.

Conclusion: A mindfulness-based stress reduction program led to enhanced abilities in mindfulness and emotional awareness and improved physical health in FND patients. Overall, these preliminary results may suggest that the improvement of subjective physical health is due to changes in interoception. In order to elaborate the potential of MBSR as treatment in patients with FND, still more research is needed.

Keywords: multiple sclerosis, immunotherapy, sex differences, age differences, fingolimod, relapse rate

Sex- and age-specific efficacy profiles of fingolimod and dimethyl fumarate in the treatment of relapsing multiple sclerosis

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Introduction: Multiple sclerosis (MS) is a chronic, autoimmune-demyelinating disease of the central nervous system. One cornerstone of treatments are disease-modifying immunotherapies of which fingolimod and dimethyl fumarate are widely used, orally available and approved for relapsing MS. Although MS affects women more frequently and they exhibit differences in disease course as compared to men, the question of sex-specific efficacy and side effect profiles of different immunotherapies has been widely neglected in clinical trials.

Aim: To investigate possible sex- and age-specific efficacies of fingolimod and dimethyl fumarate on MS-relapse rate.

Methods: Retrospective data analysis of patient cohorts.

Results: In this analysis (n=616), we demonstrate higher relapse rates in women treated with fingolimod as compared to men (adjusted hazard ratio 2.4 (95%-CI 1.2-4.6)). This could not be shown for dimethyl fumarate (1.1 (0.7-1.9)). Analyzing female fingolimod patients stratified by age (≤45 vs. >45 years), the sex-specific effect can only be demonstrated in younger women (3.3 (1.5-7.1)).

Conclusion: In this pilot report, we demonstrate a sex-specific difference of MS-relapse rate of fingolimod that is not present in the comparator dimethyl-fumarate. The difference is dependent on female sex and younger age in female patients. This possibly reflects a hormonal influence on the metabolism of fingolimod, a prodrug that requires phosphorylation via sphingosine kinases. Differences in sphingosine-1 phosphate plasma-levels, the main molecular target of fingolimod, have shown to be dependent on sex and estrogen-levels. We will further investigate in this topic refining our clinical dataset (disability progression, MRI-outcomes), sphingosine-1 phosphate plasma-levels and experimentally in a murine model system.

Abstracts for selected Symposia
Keywords: Spatial Attention, Neglect, Virtual Reality, Multimodal Cueing

Preliminary results of a feasibility study for a new virtual reality-based audio-tactile cueing-system to guide visuo-spatial attention in neglect patients

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Background: Spatial attention is an important feature for filtering everyday inputs. The direction of the attention can be guided by the use of visual, auditory or tactile stimuli. The literature regarding the effect of cueing spatial attention in visual search tasks consistently shows an improvement in accuracy and reaction time. Even though most studies have used two-dimensional setups, for which ecological validity may be questioned, there are as well studies showing the same for spatial cueing in virtual reality.

Aim: In this study, we investigated the feasibility and performance of a virtual reality-based setup with stroke patients with neglect. We examined the usability and compared the performance in a visual search task as auditory, tactile or combined cues were given.

Methode: The virtual reality system consisted of two main components, a cableless head-mounted display to present the virtual environment and a hand-held controller for the interaction. The task the participants had to solve was a simple visual search task where the objects appeared on either the left or the right side. The spawning happened in 4 conditions: No cue, auditory cue only, tactile cue only, audio-tactile cues. So far 15 neglect patients were measured with a mean age of 55.years.

Results: First of all the results revealed high usability with no side effect. Second, the performance showed the typical neglect specific behaviour when no cue was given and a tendency for normalization of this search behaviour if cues were given.

Conclusion: With this preliminary results the study shows that the developed visual search task in the tested system is well-accepted, feasible and it does not evoke any negative reactions. Furthermore, the results let assume that the cues lessen the severity of the neglect symptoms, respectively can successfully guide neglect patients to the impaired side. If these findings are consistent until the end of the study, this system would be a possible tool for guidance in visual search tasks in neglect rehabilitation.

Group 2 – Neurological Disorders 1

Abstracts for selected Symposia
Keywords: Epilepsy, Optogenetics, GABA, Seizure

Cortical excitability as a marker of epileptic seizures susceptibility in the mouse hippocampus

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Background:

Epileptic seizures are characterized by paroxysmal pathological activity of neurons. They may occur spontaneously in the epileptic brain or be triggered by conditions perturbing neuronal homeostasis even in a healthy brain.

The episodic nature of seizures, with normal or subnormal neural activity in between, indicates fluctuation of seizure susceptibility across time. However, the exact nature of this fluctuation, and the methods to measure it, remain to be determined.

Aim:

Using optogenetic stimulation of in vivo mice entorhinal neurons projecting to the hippocampus, we aim at characterizing the correlation between cortical response to short perturbations and seizure threshold.

Methods:

We developed a circuit-specific model of optogenetically induced “on-demand” seizures, by targeting entorhinal neurons which project to the CA1 with an intersectional viral approach.

We measured the EEG response of theses neurons to paired pulses of light as a biomarker of cortical excitability, and compared its variations with seizure threshold. We used the duration of optogenetic stimulation needed to elicit a seizure as a measurement of the seizure threshold (“time-to seizure”). We then explored how these markers varied in the presence of drugs modifying cortical excitability. We used serial i.p. injections of Diazepam and Pentylenetetrazol (PTZ), which are respectively GABA-A receptor agonist and antagonist, to artificially vary cortical excitability and seizure threshold.

Results:

In this preliminary study we found time-to-seizure in the presence of Diazepam, which confirms that this method can be used to quantify the seizure threshold. Moreover, cortical responses to optogenetic paired pulses decreased from a ratio of 1.2 (facilitation) to a ratio of 0.8 (inhibition) for inter-pulse intervals lower than 30ms, correlating with increases in seizure threshold. We did not find any major effect of PTZ on these metrics.

Conclusion:

Probing cortical excitability using very short perturbation of ongoing activity may be a good indicator of the current cortical excitability state, at least towards inhibition. Our model of optogenetic “on demand” hippocampal seizures could be useful to investigate the nature and the determinants of seizure susceptibility.

Keywords: Epilepsy, circadian, cycles

Chronotypes in focal epilepsy

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Epilepsy is a common neurological disorder characterized by seizures that seem to occur randomly. Yet, chronic electroencephalography (cEEG) has revealed that brain activity in epilepsy has a temporal structure involving about-daily (circadian) and multi-day (multidien) cycles of interictal epileptiform activity (IEA) and seizures. Leveraging this structure for clinical applications, such as seizure forecasting, depends critically on the prevalence of these cycles and on the distribution of multidien periodicities across individuals, which are unknown. Here, using long-term cEEG (median 5.9 y) and seizure diaries from participants in clinical trials of a brain responsive neurostimulator (N=222), we identified “seizure chronotypes,” temporal patterns of seizure timing common across individuals. Circadian cycles of seizures were highly prevalent (89%) and showed five peaks across subjects: morning, mid-afternoon, evening, early night, and late night. Multidien cycles of IEA were also highly prevalent (60%), and periodicities centered around several peaks: 7, 15, 20, and 30 days. A minority (12%) of subjects showed weak about-yearly (circannual) cycles of seizures with seasonal preference. Independent of peak circadian time or multidien period length, clinical (self-reported) and electrographic seizures consistently occurred during the days-long rising phase of IEA cycles. The strength (phase locking value (PLV) mean ± SD) of circadian (0.34 ± 0.18) and multidien (0.34 ± 0.17) cycles of seizures were comparable, whereas circannual cycles were weaker (0.17± 0.10). Our findings establish the existence of chronotypes in focal epilepsy, underscoring the power of cEEG to reveal temporal patterns of seizure timing. The high prevalence of seizure cycles in this large cohort suggests the feasibility of using these cycles as biomarkers for seizure forecasting.

Keywords: motor network, stroke, pediatrics, motor function, brain injury

The reorganization of the motor network after childhood stroke: A multimodal approach including resting state functional MRI and transcranial magnetic stimulation

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Background

To develop individualized motor rehabilitation, knowledge of the neuroplastic processes after childhood arterial ischemic stroke (AIS) is crucial. To this purpose, we can use resting-state functional MRI (rsfMRI) and Transcranial Magnetic Stimulation (TMS). While rsfMRI depicts functional connectivity between cortical networks at rest, their function can be directly determined with TMS. The connectivity within each and between hemispheres have been put forward as important mechanisms. Combining both methods may help to understand the motor network reorganization after childhood AIS. Here, we explore the relation between functional connectivity (FC), corticospinal tract excitability and interhemispheric inhibition/facilitation and their impact on hand strength.

Methods

Thirteen children and adolescents (mean age 15y 3m, range 9y5m-23y2m) diagnosed with AIS (diagnoses >2y) resulting in hemiplegia, underwent an MRI to calculate lesion size (damaged brain tissue/total brain volume) and rsfMRI to estimate FC of the motor network within and between hemispheres. Single-pulse TMS evaluated the excitability of each corticospinal tract. Paired-pulse TMS assessed interhemispheric inhibition/facilitation. Hand strength was measured with a dynamometer and we calculated the asymmetry index between hands. We investigated the relationship between i) interhemispheric connectivity and interhemispheric inhibition/facilitation, ii) intrahemispheric connectivity and cortical excitability, and iii) the motor network measures and motor function. Partial correlations (controlling for lesion size) were interpreted as absent (<0.25), fair (0.25-0.50), moderate (0.50-0.75) or excellent (>0.75). Analyses were performed in jamovi 1.6.1.

Results

Higher interhemispheric connectivity fairly correlated to interhemispheric facilitation in the stroke-to-nonstroke direction and moderately related to inhibition in the nonstroke-to-stroke direction. Higher intrahemispheric connectivity was moderately related to cortical excitability in the non-lesioned hemisphere. Larger hand strength asymmetry was fairly associated to reduced excitability of the lesioned hemisphere. There was no relation between interhemispheric inhibition in any direction and hand strength asymmetry.

Conclusion

This multimodal neuroplasticity model of the motor network illustrates how, after childhood AIS, interhemispheric inhibition/facilitation and cortical excitability may affect cortical networks and motor function. Such exploration of neurological factors highlights the complexity derived from pediatric stroke and their evaluation after a treatment may help in delineating individualized treatments.

Keywords: Epilepsy, Cortical Excitability

Probing cortical excitability in humans with epilepsy

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Epilepsy is a neurological disorder characterized by recurrent seizures. Classically, it is thought of a network of abnormally high cortical excitability (CE) within a relatively normal brain. The successful surgical removal of this pathological network hinges upon the precise delineation of the epileptic tissue, which can be done by intracranial EEG. In addition, we hypothesize that actively probing the cortex, through the injection of small electrical currents over the same electrodes, will enable more precise localization of the epileptic focus.

In this study, we use a customized software interface to commercially available hardware to enable flexible repeated pulse stimulations over long durations (24-hours). We used two protocols to analyze the effect of different stimulation parameters on cortico-cortical evoked potentials (CCEP). (P1) We use single pulse electrical stimulations (SPES) with intensities ranging from 0.2 – 10 mA to calculate an input-output curve. (P2) We use iterative paired pulse electrical stimulations (PPES) over 24 hours with time between the two pulses ranging from 10 – 1000 ms (inter-pulse interval, IPI) and measure the second response that we compare to SPES of identical intensity. In (P2), the first pulse acts as a conditioning pulse that changes the ongoing cortical dynamics and its effect on the CCEP after the second pulse can be measured.

SPES in one patient demonstrate non-linear relationship between stimulation current and amplitude of CCEPs resulting in a sigmoid curve with floor (~0.5 mA) and ceiling effects (7 mA). PPES in two patients demonstrate nonlinear dynamics, with dependence on the current conditions of the brain network. PPES with IPI ranging from 10 – 25 ms lead to intracortical suppression as compared to the reference. PPES with IPI ranging from 30 – 250 ms, at times, lead to intracortical facilitation depedning on current vigilance.

SPES and PPES are simple means of probing different aspects of cortical excitability, including flooring and ceiling effects, as well as intracortical suppression and facilitation. Investigating the fluctuations of cortical excitability based on different parameters will improve the understanding of non-linear dynamics of human neural networks in health and disease.

Keywords: Schizophrenia, Paranoia, Interpersonal Distance, Social Functioning, Aggression

Paranoia and aggression is associated with poor social functioning in first- and multiple-episode schizophrenia patients

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Background: Paranoia is a central feature of schizophrenia, is frequently present in early psychosis, and is thought to be associated with poor social outcome. However, whether a behavioral marker of paranoia – increased interpersonal distance – is associated with poor social functioning is unknown. In addition, whether this is already the case early in the course of the disease is unclear. Therefore, here we tested whether paranoia, interpersonal distance, and aggression is associated with poor social functioning in schizophrenia. Furthermore, we hypothesized that this effect can already be detected in first episode psychosis.

Methods: Our main objective was to detect the effect of paranoia, negative symptoms, and aggression on social functioning. We therefore assessed paranoia, interpersonal distance, aggression, negative symptoms, and social functioning in 64 schizophrenia patients (including 24 first episode patients) with clinical rating scales, and a behavioral marker of paranoia. Ratings of the scales, as well as the behavioral marker of paranoia, were entered in a principal component analysis (PCA). Next we tested the association of the detected factors of the PCA with social functioning applying multiple regression analysis. Furthermore, we tested the association of the detected factors and social functioning in first episode patients.

Results: The PCA yielded 3 factors explaining a total of ~67% of the variance. (1) Paranoia (~34%, including interpersonal distance and rating scales of paranoia) (2) negative symptoms (~18% including the rating scale for negative symptoms) and aggression (~16% including rating scales for aggression). Paranoia and aggression was associated with poor social functioning. This held true in first episode patients.

Discussion: Here we show that paranoia and a behavioral marker of paranoia (increased interpersonal distance) as well as aggression was linked to poor social functioning in schizophrenia. Moreover we show for the first time that this effect is already prone at the very early stage of the disease. This is of particular relevance for patients as it highlights the need for early detection and treatment of paranoia in schizophrenia to prevent an early decline of social functioning in these patients.

Keywords: astrocytes, astrogliosis, white matter injury, inflammation, preterm birth, immunopanning

Deciphering astrocyte polarization in perinatal white matter injury and its role in disease pathogenesis

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Introduction

White matter injury (WMI) is the most common form of brain injury in preterm infants and a major cause of long-term neurological morbidity. WMI is characterized by reactive microgliosis and astrocytosis, defective oligodendrocyte maturation, and in severe cases, neuronal death. Recent studies in the mature brain highlight the formation of diverse reactive astrocyte subtypes with contrasting roles after injury, some capable of mediating brain repair and other “inflammatory” reactive astrocytes with toxic functions causing myelination failure and neuronal death. At present, the specific nature of astrocyte reactivity after WMI remains obscure. We hypothesize that inflammatory astrocytes play a central role in WMI and may be an exciting therapeutic target for this disease. Here we report the results of experiments aimed to investigate inflammatory astrocyte formation in WMI.

Materials and Methods

WMI was induced in two day-old rat pups using a combination of hypoxic-ischemic and inflammatory insults. In situ hybridization with probes for inflammatory astrocyte-specific mRNA transcripts was performed on brain tissue from injured and healthy neonatal rat brains at multiple post-injury timepoints. To confirm white matter injury, immunohistochemistry (IHC) was performed on injured and healthy postnatal day 11 rat brains. We used immunopanning to purify astrocytes from the brains of injured and healthy rats. mRNA isolated from these cells was used for microfluidic qRT-PCR analysis using a panel of known markers of reactive astrocyte subtypes.

Results

In situ hybridization experiments demonstrate a significant increase in the prevalence of inflammatory astrocytes in subcortical white matter tracts in our rodent models of perinatal WMI. IHC showed the severity of the WMI produced by each model. An astrocyte immunopanning protocol optimized for our disease model yields acutely purified viable primary astrocytes, demonstrated by the expression of astrocyte markers.

Conclusion

We demonstrate the formation of inflammatory reactive astrocytes in rodent models of WMI. This result is an important step towards understanding astrocyte polarization in WMI and opens the door to experiments investigating whether prevention the formation of this astrocyte subtype ameliorates WMI disease outcomes.

Investigating the spinal circuitry in C9orf72-associated Amyotrophic Lateral Sclerosis (ALS)

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Amyotrophic Lateral Sclerosis (ALS) is a fatal motor neuron disease characterized by progressive loss of motor neurons (MNs) in the spinal cord, motor cortex and brain stem. There is no cure and few treatments are available for this disease, which affects 6-7 per 100 000 people in Europe. Patients usually live only 3-5 years post diagnosis, which further highlights the need for understanding disease-causing mechanisms and developing effective therapies.

Although the underlying mechanisms of ALS onset are unknown, sporadic and familial cases share similar clinical-pathological hallmarks such as muscle atrophy, weakness, speech and swallowing disabilities, paralysis and cognitive dysfunction, which are caused by failure of neurotransmission in the affected areas – brain, spinal cord and neuromuscular junctions. Recent studies on mice expressing mutant forms of superoxide dismutase 1 (SOD1) associated with familial ALS show that, contrary to FF MNs, S MNs display early neuroprotective hyperexcitability. MN hyperexcitability is also detected in patients during early stages of disease, which often diminishes at later stages.

Here we aim to understand if spinal MNs of mice expressing hexanucleotide repeat expansion of GGGGCC in the C9ORF72 gene, which has been identified as the most common ALS- associated mutation, display presymptomatic synaptic and neuronal excitability changes that contribute to disease onset and progression.

Using immunohistochemistry techniques, we observe that spinal MNs in C9orf72 BAC mice have higher density of excitatory cholinergic synapses (C-buttons) at young age compared to WT mice. On the contrary, at older ages, C9orf72 spinal MNs display less C-button-mediated synaptic contacts than WT MNs. Altogether, this data indicates that spinal C9orf72 MNs may display early hyperexcitability and late hypoexcitability. In addition, preliminary results suggest that FF MNs of healthy mice have more excitatory cholinergic synaptic contacts than FR/S MNs, which is not observed in C9orf72 BAC mice. This could indicate that potential reduced excitability of FF MNs in diseased mice may contribute to their specific early degeneration. We will validate these results by electrophysiological measurements and aim to modulate spinal MN activity via pharmacogenetic approaches, followed by identification of activity- dependent molecular changes in diseased MNs.

Keywords: Paranoia, Childhood Trauma, Interpersonal Distance, Schizophrenia, Safety Behaviour

Increased safety behaviour in schizophrenia and paranoia is associated with childhood trauma

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Background: Paranoia is a key feature of schizophrenia spectrum disorders. Paranoia is found in up to 80 % of schizophrenia patients, causes significant distress and triggers safety behaviors. Paranoia can be assessed with a behavioral marker – interpersonal space (IPS) – the safe area around us. Recently, it was demonstrated, that increased IPS in healthy adults was associated with childhood trauma. Here, we therefore tested whether paranoia in schizophrenia patients and childhood trauma is associated with increased IPS.

Method: In total, we included 66 schizophrenia patients and 22 healthy control subjects. We assessed childhood trauma with the childhood trauma questionnaire (CTQ) and IPS with the interpersonal distance and the fixed distance task. The interpersonal distance task consists of four conditions (active and passive approach with and without eye contact). The fixed-distance task assessed evaluation of comfort at given IPS of 0.5, 1.0, 1.5, 2.0 and 2.5 m. Our main interest was the effect of childhood trauma on IPS. Therefore, we tested group differences between low, medium and severe CTQ-groups of the interpersonal distance task with repeated measures ANCOVAs including the minimum tolerated IPS and the factors approach and eye contact. Likewise, repeated measures ANCOVAs of the fixed-distance paradigm included ratings of comfort and the factor distance to test group differences.

Results: Mean IPS was significantly associated with global CTQ scores as well as three CTQ subdomains. Furthermore, post-hoc pairwise comparisons indicated increased IPS in the high CTQ compared to the low CTQ group at trend level. Finally, comparing comfort ratings at fixed-distances yielded significant decrease in comfort ratings for the high and medium CTQ group, compared to the low CTQ group.

Discussion: Here we show for the first time that childhood trauma is associated with increased need for safety seeking in schizophrenia patients with paranoia. Our findings are of particular interest for patients, as increased safety seeking and the link with childhood trauma may have a critically impact on social functioning and calls for alternative treatment strategies.

Keywords: Endothelial Progenitor Cells, paracrine factors, cortical neuronal stem cells, microglia

Paracrine factors from endothelial progenitor cells exert neuroprotection on cultured cortical neuronal stem cells

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Stem and progenitor cells secrete trophic factors that have potential for repairing injured tissues. We have previously reported that the conditioned medium (CM) obtained from Endothelial Progenitor Cells (EPC) cultures protects striatal neurons against a toxic insult. In the present study we investigated the effects of EPC-CM on cortical neuronal progenitor cell function and / or survival. EPC were isolated from peripheral blood of healthy human donors. Primary cultures of cerebral cortex from fetal rat embryonic day 14 were treated with EPC-CM and challenged by glucose and serum deprivation. We observed that EPC-CM treatment significantly increased total cells number and cell viability in the cultures. Similarly, the number of Iba1 expressing cells was significantly upregulated by EPC-CM, while Western blot analyses for the astroglial marker GFAP did not show a significant difference. Importantly, the number of beta-lll-tubulin positive neurons in the cultures was significantly augmented after EPC-CM treatment. In line with this observation, Western blot analyses for beta-III-tubulin showed significant higher signal intensities. Furthermore, EPC-CM administration protected neurons against glucose and serum deprivation induced cell loss. In sum, our findings identified EPC-CM as a means to promote viability and/or differentiation of cortical neurons and suggest that EPC-CM might be useful for neurorestorative approaches.

This study was supported by the Swiss National Science Foundation NRP63 and the HANELA Foundation, Switzerland.

Keywords: Delirium, intensive care, critical care, virtual reality, movement patterns

Movement Analysis and Virtual Reality Stimulation to Predict and Prevent Delirium in Critically Ill Patients: Study Protocol for a Randomised Clinical Trial

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Background

Delirium has long been considered a major contributor to cognitive impairments and increased mortality following a critical illness. Both pharmacologic and non-pharmacologic strategies are currently used against delirium in the intensive care unit (ICU), despite both remaining controversial. Previous studies have shown the feasibility of using virtual reality within the ICU setting and the current proposal is to use this technology to investigate the effect of immersive virtual reality stimulation on the incidence of delirium in the ICU. Additionally, we propose to use wearable and ambient sensors, to determine if patient movement patterns can lead to early prediction of delirium onset.

Aims

The two main aims of this randomized clinical trial focus firstly on determining the effect of virtual reality stimulation on the incidence of delirium, and secondly on analysing movement patterns in order to obtain indicators of the occurrence of delirium.

Study Design

This study is conducted as a randomized clinical trial. A total of 920 critically ill patients in the ICU will participate. The control group will receive standard ICU care. The intervention group will, in addition to the standard ICU care, receive relaxing 360-degree immersive virtual reality content played inside a head-mounted display with noise cancelling headphones three times per day (morning, midday, and evening), for 30 minutes each time. Participants will be included up to a maximum of 14 days. The first 100 patients, regardless of their group, will additionally have their movement patterns recorded using wearable and ambient sensors.

Implications

It is believed that by isolating participants from commonly occurring disturbances in the ICU through virtual reality stimulation, the incidence of delirium will be decreased, leading to fewer long term health problems. Moreover, identifying movement patterns associated with delirium could allow for early detection and intervention, potentially decreasing the long term negative outcomes associated with delirium.

Conclusions

Delirium is widely present within the ICU setting but lacks validated prevention and treatment strategies. Investigating the effect of virtual reality on the incidence of delirium, and the possibility of identifying delirium onset through movement patterns could prove to be valuable detection and prevention strategies.

Group 3 - Neurological Disorder 2

Abstracts for selected Symposia
Keywords: Cerebellum, SCA1, TrkB

Deciphering developmental connectivity deficits in Spinocerebellar ataxia type-1

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Spinocerebellar ataxia type 1 (SCA1), is a debilitating and fatal neurodegenerative disease (ND) caused by an abnormal polyglutamine (PolyQ) tracts expansion in the protein Ataxin-1. Despite the ubiquitous expression of the mutated protein from birth on, its toxicity and related pathological consequences are observed only in patients in their mid-thirties, suggesting the presence of a compensatory / adaptive response that may precede and delay the pathology. During the disease course, the optimal functioning of cerebellar circuit is strongly compromised, leading to a consequential vulnerability of Purkinje cells (PCs). This vulnerability is reflected by the early morphological and structural alterations in the presynaptic excitatory inputs arising from climbing fibers (CFs) with concomitant changes in PC excitability, followed by a late prominent loss of PCs. These observations suggest the existence of predefined disease susceptible components within the cerebellar circuit. Despite the advancement in the discovery of affected molecules and cellular pathways in SCA1 pathology, the mechanism leading to CF impairments as well as the consequences of these alterations within PCs and their impact on disease progression remains unclear. Using transgenic mice model of SCA1, we investigated early molecular changes that may determine the suboptimal functioning of the cerebellar circuit and eventual PC degeneration. At presymptomatic disease stage, we identified the early and pronounced reduction in Tropomyosin receptor kinase B (TrkB) expression; a key molecule involved in CF maturation and optimal PC function. By applying morphological analysis of the cerebellar cortex structure, behavioural testing of motor performance and ex vivo electrophysiological recording, we are currently deciphering its potential role in SCA1 pathophysiology. To this end, we have enhanced TrkB expression either in PCs or CFs by employing cell type-specific Cre mouse lines, with the aim to investigate the contribution of TrkB to the pathology and explore its neuroprotective effects in dampening SCA1 symptoms

Abstracts for selected Symposia
Keywords: gesture, schizophrenia, psychosis, functioning, social interaction

Gesture deficits affect overall functioning in patients with schizophrenia

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Introduction

Gestures are a crucial feature of nonverbal communication as they convey information either by themselves or together with speech, facilitating understanding during social interactions. Schizophrenia patients produce fewer gestures during social interactions. This can have severe consequences to patients' social and global functioning in society. Here, we measure gesture performance in patients with schizophrenia and examine how it relates to their overall functional capacity and outcome.

Methods

We included 20 patients with schizophrenia (mean age = 41.81 years; SD = ± 14.30; 50% male). Gesture performance was assessed using the well-established Test of Upper Limb Apraxia (TULIA). TULIA measures gesture performance in two domains: *imitation* following demonstration, and *pantomime* following verbal command. Total score of TULIA ranges from 0-240. In addition, functional capacity was assessed with the brief version of the University of California San Diego Performance-Based Assessment (UPSA brief), which tests the ability to use everyday skills relevant for functioning, while global functional outcome was measured with the Global Assessment of Functioning (GAF).

Gesture performance highly correlated with age (rho = -.56; p <.01), thus we used partial correlations (covaried for age) to assess the relationship between gesture performance and functional capacity/outcome.

Results

Patients had a mean total TULIA score of 195.05 ± 21.80, suggesting severe deficits in gesture performance. Gesture deficits were higher for pantomime (92.8 ± 10.75) than imitation (102.25 ± 12.47). In addition, gesture performance highly correlated with both functional capacity and functional outcome (rho values > .56, p <.05). Although, gesture performance in both domains (imitation and pantomime) correlated with functional outcome (rho values > .48, p < .05), only pantomime significantly correlated with functional capacity (rho = .70, p < .01), whereas imitation was at trend level (rho = .41, p = .08).

Discussion

We show that gesture deficits are prevalent in patients with schizophrenia, and that they are directly related to their overall functional capacity/outcome. This highlights the importance in alleviating gesture deficits in patients with schizophrenia using brain stimulation, virtual reality and cognitive remediation therapy to further improve their quality of life.

Abstracts for selected Symposia

Keywords: Parkinson's disease, substantia nigra, Nogo-A, dopaminergic neurons, human

Co-expression of Nogo-A in dopaminergic neurons of the human substantia nigra pars compacta is reduced in Parkinson's disease.

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Parkinson's disease is mainly characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta that eventually leads to a depletion of dopamine in the striatum. These dopaminergic neurons are particularly vulnerable against various insults including oxidative stress. Importantly to note, characteristic for Parkinson's disease is a progressive cellular deposition of alpha-synuclein in dopaminergic neurons in the substantia nigra likely contributing substantially to their cell loss. There is growing evidence that Nogo-A may be critically involved in neuropathological and neurodegenerative conditions. In line with this notion, we recently demonstrated that Nogo-A expressing cells are found in the rat substantia nigra and that around half of the number of dopaminergic neurons co-express Nogo-A. Importantly, we reported for a higher survival of dopaminergic neurons in the substantia nigra co-expressing Nogo-A in an animal model of Parkinson's disease. These observations let us speculate that Nogo-A may be neuroprotective for dopaminergic neurons in the course of Parkinson's disease. In collaboration with the Translational Research Unit, we developed a tissue micro array (TMA) that allows for simultaneous staining of a large number of tissues in a single run. Interestingly, and in contrast to the observations gathered during normal ageing and in the animal model of Parkinson's disease, increasing age was significantly associated with a lower co-expression of Nogo-A in nigral dopaminergic neurons of patients with Parkinson's disease. In sum, while Nogo-A expression in dopaminergic neurons is higher with increasing age, the opposite is the case in Parkinson's disease. These observations suggest that Nogo-A plays a substantial role in the vulnerability of dopaminergic neurons in Parkinson's disease.

Abstracts for selected Symposia

Keywords: depression, psychomotor disturbance, actigraphy, preliminary data

Observer-based rating of agitation predicts naturalistic activity in major depression

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Background: Psychomotor disturbance (PmD) is a common symptom cluster in major depressive disorder (MDD), one of the leading causes of burden of disease worldwide. PmD is associated with more severe depression and worse treatment response. Therefore, it is crucial to identify and quantify PmD reliably. However, this is challenging as PmD consists of seemingly opposing psychomotor agitation (PmA) and retardation (PmR), which can be present simultaneously. The core assessment of psychomotor disturbance (CORE) aims at quantifying PmA and PmR. This scale is based on observed behaviour during an interview. A naturalistic alternative to observer-rated scales is actigraphy, which measures activity using an accelerometer. In this preliminary analysis, we aimed at testing the agreement on PmD of actigraphy measures and CORE.

Methods: Depressed and remitted participants were recruited in Chicago, USA. We completed CORE ratings for each participant based on a videotaped structured interview. After the study visit, participants wore a wrist-actigraph for two weeks. Actigraphy-timeline was automatically classified into active periods and rest periods. We correlated CORE subscales with the total accelerometer counts per active period and per day, as well as with the average counts per minute for active periods and whole days, respectively.

Results: This sample of 9 participants was predominantly agitated. Analyses revealed strong significant positive correlations of CORE-PmA subscale with total accelerometer counts per day, and total counts and counts per minute during active periods. We also observed consistently negative correlations of CORE-PmR subscale with actigraphy measures, however, none of these reached significance.

Discussion: The association of CORE-PmA subscale with higher total activity and higher frequency of activity in our sample validates the observer-based scale by an objective and naturalistic measure. Correlations of PmR with actigraphy measures were consistently negative, indicating that PmR is associated with reduced total activity and frequency of activity. The lack of significant results in PmR might be due to predominant agitation and the small size of this sample. Furthermore, this is preliminary data lacking a comparison with healthy controls. Actigraphy may become a low-cost assessment for longitudinal studies, reducing the need for in-person visits.

Keywords: motor abnormalities, schizophrenia, psychosis, functional outcome, functioning

Motor abnormalities are associated with poor social functional outcomes in schizophrenia

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Background: Aside from cognitive and affective symptoms, patients suffering from schizophrenia (SCZ) often show impaired motor behavior. SCZ patients with motor abnormalities have reduced quality of life, impaired work capacity as well as decreased life expectancy by 10-20 years. The impact of motor abnormalities on global and social functional outcomes is not clear yet. We hypothesized, that the presence of motor abnormalities is associated with poorer functional outcomes in SCZ patients.

Methods: We included 90 patients suffering from SCZ spectrum disorders and collected data on 5 types of motor abnormalities: (i) Parkinsonism using Unified Parkinson's Disease Rating Scale (UPDRS III); (ii) Catatonia using the Bush Francis Catatonia Rating Scale (BFCRS); (iii) Dyskinesia using the Abnormal Involuntary Movement Scale (AIMS); (iv) Neurological soft signs using the motor coordination subscale of the Neurological Evaluation Scale (NES); and (v) Psychomotor Slowing using the Salpêtrière Retardation Rating Scale (SRRS). Furthermore, we used three different scales to evaluate the functional outcomes: two using clinicians' judgment (i) the Global Assessment of Functioning (GAF); (ii) the Social and Occupational Functioning Assessment Scale (SOFAS); and one using a performance-based measure of functional capacity, i.e. the brief version of the UCSD Performance-based Skills Assessment (UPSA-B).

Results: Our analyses demonstrated that there are statistically significant negative correlations between UPDRS, BFCRS, NES and SRRS with both GAF (all rho >-0.24, p-value <0.05) and SOFAS (all rho >-0.25, p-value <0.05) but not for the UPSA scale (all rho <-0.22, p-value > 0.14). Finally, there are no significant correlations between AIMS and any of the functional outcome scales (all rho <0.11, p-value >0.37).

Discussion: Here, we showed that four of the most common motor abnormalities observed in schizophrenia negatively impacted the patients' functional outcomes. The stronger the motor impairment was the worse was the global and social functioning. However, none of the motor scales correlated significantly with UPSA suggesting that motor abnormalities were not associated with functional capacity. In conclusion, in schizophrenia, motor impairments seem to be associated with poor global and social functioning suggesting that improving motor performance in schizophrenia patients might improve patients' quality of life.

Keywords: coma, phase-locking, lempel-ziv, spectral exponent, outcome

Electrophysiological dynamics of auditory processing in postanoxic comatose patients

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Auditory processing is preserved in the absence of consciousness, such as in the comatose state. Previous studies have shown a strong link between the integrity of auditory processing and coma outcome, so that an increase in auditory discrimination is associated with recovery. However, the electrophysiological dynamics of auditory responses in coma and their link to outcome remain under-explored. Here, we assessed the dynamics of EEG responses to auditory stimuli using phase-locking value, which quantifies phase consistency of EEG responses across electrodes and Lempel-Ziv complexity, quantifying the complexity of EEG responses in time. We also explored the background decay of the power spectrum – the spectral exponent, a metric of neuronal noise, – which has been shown to be steeper in other non-conscious states like anesthesia.

We calculated these measures on auditory-evoked EEG activity in 13 healthy controls and 67 postanoxic comatose patients, retrospectively labelled as survivors (N=41) and non-survivors (N=26), during the first day of coma, and split into pilot and validation groups.

Phase-locking value was significantly higher for survivors (M=0.74, SD=0.07) compared to non survivors (M=0.61, SD=0.09), t(26)=3.9, p<0.01. and was a predictor of favorable outcome, achieving a positive predictive value of 83% in our validation group. Lempel-Ziv complexity was significantly lower for comatose patients than controls, U(67, 13)=290, p<0.05, however not statistically different between survivors and non survivors. The spectral exponent was steeper for comatose patients than controls, t(78)=3.38, p<0.01, and also significantly steeper for patients with a favorable outcome, t(65)=2.24, p<0.05.

Higher phase locking and steeper spectral exponent in survivors than non-survivors during hypothermia may be indicative of more structured responses to auditory stimuli across time and electrodes. Future investigations will link these metrics to other states of reduced consciousness and identify their relevance for predicting the outcome of postanoxic comatose patients.

Keywords: dysautonomia, orthostatic intolerance, cognitive impairment, water intake, alertness, divided attention, working memory

Orthostatic Cognitive Dysfunction in Postural Tachycardia Syndrome After Rapid Water Drinking

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Background: Postural tachycardia syndrome (POTS) is a form of autonomic dysregulation and is characterized by an excessive heart rate increment upon the upright body position while blood pressure is maintained. Patients experience typical symptoms of orthostatic intolerance such as dizziness, nausea and cognitive impairments. The present study assessed position-dependent attentional and cognitive functioning in POTS patients compared to healthy subjects and tested the response of cognitive performance to acute water intake.

Methods: Data was obtained from eight patients with neuropathic POTS and eight healthy subjects of similar age and gender. All participants completed questionnaires that assessed health-related quality of life and depression and underwent four rounds of neuropsychological testing overall, each before and after the intake of 500 ml still mineral water and both in the supine and in the upright posture.

Results: POTS patients showed deficits in working memory exclusively in the upright position compared to healthy subjects, but no position-dependent impairments in alertness or divided attention. Rapid water ingestion had a beneficial effect on working memory in the upright posture, lead to a decrease in heart rate increment and to an improvement of subjective symptom experience.

Conclusion: The results provide support for the occurrence of purely orthostatic cognitive deficits in POTS, especially when increased executive control and cognitive resources are required and document a favorable effect of water intake on cognitive performance. These findings have important implications for the management of cognitive symptoms in POTS as high water intake is an easy and accessible treatment strategy.

Keywords: Functional Neurological Disorders, Cortisol Awakening Response (CAR), Stress, Hypothalamic-Pituitary-Adrenal (HPA) Axis

Altered Cortisol Awakening Response in Functional Neurological Disorders

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Background: Functional neurological disorder (FND) is a neuropsychiatric condition in which patients experience neurological symptoms in the absence of an organic disease. Those symptoms can encompass gait problems, tremor, weakness or non-epileptic seizures. Psychological and/or physical stress (e.g., stressful life events or trauma) have been considered risk factors for developing FND. However, little is known about the biological stress regulation in FND. Investigating a potential dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis in FND could shed a light on the underlying neurobiological mechanisms and might serve as a non-invasive biomarker of the disorder.

Methods: In order to examine potential alterations in the HPA axis, the cortisol awakening response (CAR), diurnal cortisol slope (DCS) and total daily output (AUCg, area-under-the-curve with respect to ground) of 16 FND patients compared to 15 healthy controls were analysed. In parallel, subjective symptom severity, experienced traumatic events and perceived subjective stress was compared in FND patients and controls as well as correlated with the biological measures.

Results: FND patients had a significantly lower CAR compared to healthy controls. Furthermore, a trend of flatter DCS was observed in FND patients when compared with healthy controls. The DCS negatively correlated with subjective symptom severity of FND patients. FND patients had significantly more experienced traumatic events and significantly higher perceived subjective stress levels than healthy controls. However, experienced traumatic events and perceived subjective stress did not correlate with the cortisol measures.

Conclusions: Lower CAR has been associated with trauma and abnormal psychosocial functioning. Furthermore, flatter DCS have been proposed as a link between psychosocial stress and poor mental and/or physical health. In summary, these preliminary results point towards an altered activity of the HPA axis in FND patients, which might represent an endophenotype of the disorder.

Abstracts for selected Symposia

Keywords: C9ORF72-ALS; ER stress, mitochondria, gene therapy

Maintaining ER- mitochondria contacts is neuroprotective in preclinical models of ALS

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Amyotrophic lateral sclerosis (ALS) is the most common motor neuron (MN) disease in adults with a prevalence of 6-7 per 100 000 people in Europe. Sporadic and familial cases of ALS share similar clinical-pathological hallmarks, involving muscle atrophy, paralysis, speech and swallowing disabilities, and cognitive dysfunction due to selective MN degeneration in the spinal cord, brainstem and motor cortex. In 2011, mutations in the *C9ORF72* gene characterized by a long hexanucleotide repeat expansion (G4C2) up to thousands of repeats, was found to be highly prevalent in familial ALS and fronto-temporal dementia (FTD). Several cellular processes have been connected to C9ORF72 ALS pathogenesis such as haploinsufficiency of the *C9ORF72* gene, repeat RNA mediated toxicity, and dipeptide protein toxicity; nevertheless, it has been challenging to delineate causal from consequential pathogenic alterations.

Previous studies from our group have shown strong evidence that endoplasmic reticulum (ER) stress and mitochondrial dysfunction are implicated in the pathogenesis of ALS. Here, we focused our attention on the early intrinsic vulnerability of motoneurons to ER stress and its repercussion on the mitochondrial-ER associated membranes (MAMs), that has been reported to be disrupted in several neurodegenerative diseases.

Using motoneurons differentiated from *C9ORF72* patients induced pluripotent stem cells (iPSCs), we have identified a linker molecule GRP75 that serves to not only physically connect the two cellular compartments, but whose transient enhanced expression has a neuroprotective effect during the progression of the pathology. Moreover, taking advantage of the newly generated *C9orf72* pre-clinical rodent model, we performed pharmacological and viral mediated modulation of ER stress and provide evidence that the ER compartment is critical for optimal mitochondrial function and restoring the physiological levels of ER stress is able to rescue mitochondrial dysfunction. Lastly, we validate the therapeutic potential of GRP75 via gene therapy using *adeno-associated viruses* (AAVs) thereby highlighting a promising therapeutic target for ALS.

Abstracts for selected Symposia

Keywords: Cognitive decline, ambient sensors, wearables, home-monitoring

Contactless Location measurements as Predictors of Cognitive State

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Recently, sensors have become ubiquitous, including in health sciences. Consequentially, the amount of data we collect from patients has multiplied enormously. A new term that has arisen in this context is *digital biomarker* – biomarkers obtained through sensor-based measurements.

With improvements in sensor technology, contactless monitoring has become easily accessible and shows higher acceptance rates by the people than other sensors. As such, they provide a good basis for the development and discovery of digital biomarkers.

The MoCA test is an important indicator of the cognitive state of people. While this point-in-time evaluation is simple to conduct, with repeated test applications memorization-effects can kick in and reduce the meaningfulness of it. Simultaneously, continuous monitoring of the cognitive state is important for older people and people in risk groups, to prevent sudden decline of health.

Here, we propose a new digital biomarker, able to continuously track cognitive state of the monitored people over long periods of time, while offering high acceptance by the people.

48 people (35 women, age 81.08 (SD 9.73), MoCA is 23.88 (SD 4.54)) participated in this study. Participants were monitored continuously over a span of four weeks, using five contactless passive infrared sensors, installed in their homes. Based on this data, a patient specific measure was developed. (Reconstruction error of eigen-vectors based on their individual location-information matrix). This new measure was correlated to the MoCA-score of the people. A linear regression and binary classifier were trained to predict cognitive state and distringuish normal cognition from MCI. The receiver-operating-characteristic (ROC) was calculated to assess the classification performance.

The Spearman correlation of our measure and the MoCA-score is $\rho = -0.65$ with a p-value < 0.001. The RMSD of the MoCA-score prediction, is RMSD = 3.43. For the classification, the area under the curve (AUC) of the ROC is AUC = 0.94.

The binary classification with an exceptionally high ROC AUC outperforms the prediction. The high acceptance of these contactless sensors together with the good results obtained in this study make this new measure a very strong candidate for a new digital biomarker to distinguish healthy from MCI patients.

Group 4 – Virtual Reality / Motor Learning / Neurological Disorders

Abstracts for selected Symposia
Keywords: Motor learning, Neurorehabilitation, VR, head mounted display, immersive virtual reality

Effects of immersive Virtual Reality on Movement Quality and Cognitive Load in young and elderly participants

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Robots can now be found in routine clinical use to engage neurologically injured patients in high-intensity and high-repetitive training. Virtual reality (VR) is employed to provide visual feedback and enhance patients' motivation during the lengthy robot-aided training. However, visualizing the movements on flat screens shifts patients' attention away from their real movements, require additional visuo-spatial transformations between the real and virtual movements, and lack depth cues. We hypothesize that these limitations might negatively impact the patients' movement quality, cognitive load, and therefore, rehabilitation outcomes.
In this study we evaluated the potential benefits of more immersive technologies using head-mounted displays (HMDs). We compared the impact of novel visualization technologies (immersive VR (IVR) and augmented reality (AR) HMDs) vs. standard computer screen (SCREEN) on movement quality and cognitive load in two groups of young and elderly healthy participants (young: 24 ± 4 y.o.; elderly: 74 ± 8 y.o.). Participants performed simultaneously a motor (i.e., reaching in 3D space) and cognitive task (i.e., counting). The targets were located to require hand movements in either one, two, or three dimensions. Movement quality was quantified through different kinematic features (i.e., movement duration, trajectory straightness, peak velocity, and smoothness). The performance accuracy in the counting task was employed to assess participants' cognitive load. We found that the movement quality improved when movements were visualized in IVR compared to the SCREEN in both age groups. The movement quality with AR was worse than with IVR and better than SCREEN, especially in the elderly group. Young participants performed straighter and smoother movements when performing one-dimensional vs. higher dimensionality movements specifically when using the computer screen, while no effect of movement dimensionality specific to a display type was observed in the elderly group. None of the age groups showed significant differences across visualization technologies in the cognitive task accuracy. Importantly, elderly participants did not report significant difference in usability between IVR and the SCREEN.
Our results provide encouraging evidence that VR-therapy interventions involving movements in several dimensions might strongly benefit from the use of immersive VR through HMDs, even in a population that is not familiar with new technologies.

Abstracts for selected Symposia
Keywords: neurorehabilitation, stroke, upper-limb rehabilitation, robotics

Clinical-Driven Development of a Robotic Device for Sensorimotor Rehabilitation

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Every year, millions of stroke survivors lose their functional autonomy due to hand and arm paralysis. Clinical evidence suggests that patients should engage in task-specific, high-intensity training to maximize their recovery. Additionally, neuroscience suggests that both realistic visual and somatic sensory information play a fundamental role in generating skillful movements. Potentially, rehabilitation robots could provide this, but current robots only provide high-intensity training for non-functional movements. Current robot-aided interventions rely on abstract visual feedback while somatic (tactile and proprioceptive) feedback is underutilized. Further, despite the increasing interest in robotics for rehabilitation, only a few robotic devices have been tested in clinical settings. Complexity (e.g., long setup times and overabundant functionalities) is the major obstacle to technology acceptance.

We address these limitations by developing a novel clinical-driven robotic device for upper-limb sensorimotor rehabilitation, which will be capable of fine render interaction forces with tangible virtual objects. Training tasks with rich rendered dynamics in an immersive virtual environment (i.e., using stereoscopic head-mounted goggles) will provide realistic sensorimotor information during motor training. The novel device will allow for simultaneous sensory and motor training and improve upper-limb functions, which are relevant for activities of daily living.

We are employing a clinical-driven approach in close collaboration with therapists from the Department of Neurology of the University Hospital Bern. We surveyed 33 participants (therapists, nurses, and physicians working in neurorehabilitation) on the clinical requirements for a new robotic device. We found that grasping, eating, and personal hygiene are amongst the most important activities of daily living to be exercised. Finger and wrist extensions were reported as crucial movements to be trained. An adjustable quantity of virtual objects and adjustable task difficulty were also highly demanded features. Importantly, the majority of the participants would like to spend less than ten minutes to set up the robotic device.

We are working towards closing the gap in sensorimotor rehabilitation as our novel affordable, effective, and quick to equip device will be one of the first to provide congruent sensations during training. This project will optimize rehabilitation and positively impact the quality of life of millions of stroke patients.

Abstracts for selected Symposia

Keywords: Motor Learning, neurorehabilitation, robotics, haptic rendering, human arm weight support

Benefits of Somatosensory Feedback During Robotic Training with Arm Weight Support

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Robots can now be found in routine clinical use for motor training of neurologically injured patients. However, current rehabilitation robots do not support patients to regain the functional movements needed to perform Activities of Daily Living (ADL), crucial to achieving functional autonomy. This is not surprising, since current robot-aided interventions rely on visual feedback while somatic (tactile and proprioceptive) feedback is overlooked. Somatic information strongly influences motor cortical activity and plays a fundamental role in generating skillful movements. Thus, robots that enhance somatic information through haptic rendering –i.e., the provision of simulated interactive forces with virtual environments– might promote neuroplasticity, especially when manipulating objects with complex dynamics –e.g., carrying a cup of coffee. However, special attention should be put on the selection of the assisting control strategy, since assisting forces may degrade the perception of the somatic feedback, and thus, hamper motor performance and learning. We propose that arm weight support might overcome this problem because it does not vary with the movement and would only minimally interfere with the haptic rendering.

We conducted a within-subject pilot study with six healthy participants to investigate the benefits of haptic rendering on motor performance. We further evaluated if arm weight support, provided by an arm exoskeleton, hinders these potential benefits. Participants were asked to invert a virtual pendulum and keep it inverted. The participants practiced the highly dynamic task with three different training modalities randomly presented: (i) only somatic feedback (i.e., haptic rendering of the pendulum dynamics), (ii) arm weight support in addition to the haptic rendering, and (iii) arm weight support without haptic rendering.

We found that adding somatic feedback did not improve task performance, but positively impacted how participants moved to achieve the task –i.e., they covered significantly more workspace with higher speeds while putting only moderate effort. The addition of arm weight support did not interfere with the haptic forces –i.e., participants did not change their movement strategy– but increased participants' task performance and reduced their effort.

We conclude that haptic rendering in addition to arm weight support is a promising robotic intervention to enhance neurorehabilitation.

Abstracts for selected Symposia

Keywords: EEG, Cognitive Neuroscience, Neuroscience, Attention, Vision, Motor Learning, Neurorehabilitation, Virtual Reality

Enforcing task rules during training to promote motor learning and modulation of attentional brain networks: an EEG study with healthy participants

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Motor learning is a complex neuronal process underlying neurorehabilitation. Cognitive (e.g., attentional) engagement is important for motor learning, especially early in the learning process. Training parameters supporting the cognitive engagement of participants – e.g., visual cues or task instructions – may be used to improve motor learning. In this study, we investigated if task instructions enforcing the underlying task rule of a virtual sailing task modulate motor learning and attentional networks engaged (reflected in alpha-band cortical activity) using Electroencephalography (EEG). Healthy participants (n = 36) were trained to surf waves as fast as possible in a virtual environment using a joystick. The explicitness of instructions was manipulated across implicit (I: participants sailed freely), explicit (E: verbally instructing them how to correctly align the boat), and explicit-implicit (EI: implicitly instructing them to move correctly using visual cues) conditions.

We found superior motor learning linked to training with explicit knowledge about the task rules (E) and with visual cues enforcing these rules (EI) compared with training without any enforcement of the task rules (I). In a period of -50 ms to 350 ms relative to wave onset, we observed that participants training with visual cues (EI) significantly enhanced alpha strength over parieto-occipital and frontal areas compared with participants training with the other task instruction conditions.

Even though participants in the Explicit and Explicit-Implicit conditions improved their motor performance, training with visual cues (EI) may be associated with cognitive facilitation – namely, a lower engagement of selective visual (parieto-occipital) and executive (frontal) attentional brain networks after training. In the light of our data, we posit that training parameters such as task instructions modulate the attentional engagement during motor learning and may be an important factor to consider in neurorehabilitation.

Keywords: neurorehabilitation, stroke, robotic, sensory, assessment, training, haptics, psychometrics

A novel robotic system for sensory training

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Approximately half of stroke survivors suffer from sensory impairments, hampering their ability to perform skilful movements. Unfortunately, due to time and personal constraints, sensory training is not the standard of care, limiting the opportunity of patients to regain functional recovery, as sensory impairment at baseline is a predictor of poor motor recovery.

In this project, we aim at developing a robotic system for sensory training that also allows for a systematic assessment of patients' sensory loss with minimal therapist supervision. We developed a robotic virtual testing environment based on the Tactile Discrimination Test (TDT) concept. The TDT is a conventional assessment approach to evaluate touch sensibility that requires the patient to explore texture gratings (i.e., active touch). Therefore, if the patient suffers from a severe motor deficit, the therapist guides patients' hands along the textures (i.e., passive touch). However, it is still an open question whether active/passive touch can equally assesses sensory impairment.

To answer this question, we deployed a robotic virtual task that consists of discriminating the "odd texture" among three visually identical textures, either with active/passive exploration. The texture gratings are haptically rendered by a Delta robot. The only difference between the odd and the other textures is the distance between virtual bumps (spatial period). The robotic device can also guide the patients' hands with haptic guidance (passive touch). We plan a within-subjects experiment with two conditions – passive and active exploration– in healthy elderly and post-stroke patients. The experiment consists of three multiday sessions. The first session comprises one baseline per active/passive condition. Each consecutive session includes three blocks (i.e., baseline, training, retention) per active/passive condition. The outcome measures are discrimination threshold, and point of subjective equality. Re-test reliability will be evaluated comparing the outcomes measured at baselines of first and second sessions/days. During training, we will gradually reduce the spatial period to challenge patients sensory ability, and provide visual feedback about their performance. We expect better touch sensibility after training and no significant differences between active/passive conditions.

Our novel robotic touch system would allow sensorimotor assessment and training with only minimal therapist supervision.

Keywords: Seizures, limbic circuit, Entorhinal, Hippocampus, optogenetics

A circuit model of limbic seizures

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Background

The hippocampus, forms recurrent connections with the entorhinal cortex (Ent), which renders the network prone to seizures. An important unresolved question concerns which critical sub-components of this circuit can elicit seizures and how seizures can propagate across the network.

Methods

We expressed channelrhodopsin specifically in glutamatergic cells of the temporoammonic pathway in four adult mice (C57/Bl6) with an intersectional viral approach. These animals were further implanted with bilateral depth electrodes in CA1, CA3, DG, Ent and Anterior nucleus of the thalamus, as well as optic fibers in the Ent and CA1. To map the targeted connections, we used fluorescent reporter genes in histology and measured delays of peaks in LFP upon single-pulse optogenetic stimulation. For seizure induction the animals received 20Hz stimulations of increasing duration alternately in CA1 and Ent every second day.

To study the spread of ictal activity we used the intrahippocampal Kainic acid (KA) model of epilepsy in six adult mice (C57/Bl6). We recorded spontaneous seizures for eight weeks and characterized the spread of the ictal activity across different nodes of the limbic circuit.

Results

We tracked single evoked potentials originating in the Ent respectively CA1 across different nodes of the Papez circuit, bidirectionally. The delay of the signal increased proportionally to the path-length to the stimulation site, while the signal to noise ratio decreased. Seizures induced in three out of four animals showed similar electrographic features, duration (Ent: mean=28.2s ±6.6, CA1: mean=26.7 ±9.8) and required similar stimulation time (Ent: mean=7.7 ±3.8s, CA1: mean=6.3s ±1.6s). In our separate cohort of epileptic animals, we observed both interictal and localized ictal activity in the left (intact) and right (KA) hippocampus, but seizures could also propagate to other nodes of the limbic circuit (e.g. Subiculum, Ent, Retrosplenial cortex)

Conclusion

We propose a highly-selective "on- demand" circuit model of seizures in the temporoammonic pathway, which is reproducing typical network features of the well-established Kainate model. We show that optogenetic stimulation of pyramidal neurons (soma or axon) in this circuit elicits seizures in freely moving, non- epileptic animals.

Abstracts for selected Symposia

Keywords: CNS barriers, neuroinflammation, macrophages, migration, polarization

Monocyte recruitment to the inflamed central nervous system: migration pathways and distinct functional polarizations

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The blood brain barrier (BBB), the blood cerebrospinal fluid barrier (BCSFB) and the blood leptomeningeal barriers are specialized anatomical interfaces which control the trafficking of immune cells towards the Central Nervous System (CNS) parenchyma and protect it from invading pathogens. During autoimmune diseases such as multiple sclerosis (MS), monocyte derived macrophages are one of the immune cell types that cross the CNS barriers and significantly contribute to the disease progression. What are the entry routes of these cells inside the CNS parenchyma during autoimmune neuroinflammation, and whether the CNS barriers influence the polarization and the further action of these cells remains unclear.

In our study, we assessed the interaction of differentially polarized monocyte-derived cells with endothelial (BBB) and epithelial (BCSFB) barriers of the CNS, in tissue sections and functionally, *in vitro*. We observed that while the migration of monocyte-derived cells across the BBB endothelium is strongly reduced upon functional polarization, pro- and anti-inflammatory macrophages can efficiently adhere and migrate towards with the BCSFB epithelium. Accordingly, *ex vivo* analysis of choroid plexuses (ChP) revealed an increased number of infiltrating macrophages in the ChP stroma and a scattered presence of polarized cells during the onset and peak phases of experimental autoimmune encephalomyelitis, a mouse model for MS. Additionally, the interaction of unpolarized macrophages with the inflamed endothelial and epithelial cell barriers induced upregulation of several genes associated with inflammation in macrophages.

Altogether, we show that the acquisition of distinct polarization profiles significantly alters the adhesive and migratory properties of macrophages across the CNS barriers.

Abstracts for selected Symposia

Keywords: MOG, EAE, FcRn, neuroimmunology, immunomodulation

Anti-neonatal Fc-receptor antibody treatment ameliorates disease course and visual outcome in antibody-driven experimental autoimmune encephalomyelitis

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Encephalomyelitis associated with antibodies against myelin oligodendrocyte glycoprotein (MOG, MOG-IgG, MOG-EM) is a recently described autoimmune demyelinating disorder of the central nervous system. The metabolism of IgG is controlled by the neonatal Fc-receptor (FcRn) preventing IgG degradation and thereby extending its half-life in the plasma. Inhibition of FcRn-mediated recycling of IgG represents an attractive treatment target in antibody-mediated diseases. The effect of FcRn blockade with a specific monoclonal antibody (αFcRn, UCB, 4470) has not been assessed in MOG-EM.

We induced active MOG_{35-55} experimental autoimmune encephalomyelitis (EAE) in C57Bl/6 mice followed by the application of a monoclonal MOG-IgG (8-18C5) 10 days post immunization (dpi). Animals were treated with either αFcRn or an IgG isotype on 7, 10 and 13 dpi. Neurological disability was scored daily according to clinical symptoms (10-point scale) and histological correlates were quantified using immunohistochemistry for immune cell infiltration, Luxol Fast Blue/PAS staining for demyelination and immunofluorescence for complement deposition. Additionally, visual acuity was assessed by optomotor reflex (OMR) measurement.

In MOG-IgG augmented MOG_{35-55} EAE (3 independent experiments, total: αFcRn n=27 vs. isotype n=24), αFcRn treatment lead to a significantly attenuated course of disease, correlating with reduced amounts of demyelination and macrophage infiltration into the spinal cord. T and B cell infiltration as well as complement deposition remained unchanged. Furthermore, αFcRn treatment prevented loss of visual acuity over the course of disease. In contrast, no difference in histopathological correlates were observed in optic nerves of MOG-IgG augmented MOG_{35-55} EAE compared to isotype-treated controls with the caveat of lower n-numbers in this part of the analyses.

We show that αFcRn treatment preserves visual function and ameliorates the course of EAE in a MOG-IgG-augmented active MOG_{35-55} EAE. Furthermore, αFcRn treatment leads to less macrophage infiltration and demyelination in the spinal cord, but not the optic nerve. Thus, selectively targeting FcRn might represent a promising potential therapeutic approach in MOG- and other antibody-mediated diseases. However, the impact of MOG-IgG augmentation and αFcRn treatment on the visual system needs further investigation.

Keywords: Motor learning, virtual reality, stroke, embodiment, EEG

First-person immersive virtual reality to improve neurorehabilitation

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Virtual reality (VR) is often used during robotic rehabilitation training following brain injury to provide a motivating and safe environment. Current rehabilitation setups usually employ computer screens to display the virtual environment. In this virtual training environment, the patient interacts via a symbolic virtual representation, for example, a cursor. In contrast, relatively novel and commercially available head-mounted displays have a great potential to realistically mimic the subject's limb in a highly immersive training environment. In this immersive VR, the symbolic virtual representation may become a self-representation (i.e., avatar), promoting the feeling of body ownership over the virtual limb. Importantly, brain areas involved in body ownership are shared with brain areas linked to motor learning, namely multimodal areas associated with motor control. Therefore, increasing body ownership using immersive VR might be an effective tool to promote brain plasticity in motor areas during training. Yet, evidence on the benefits of first-person immersive VR during motor training is missing. The aim of this study is to investigate the neural and behavioural benefits of embodying a virtual limb during robotic motor training in stroke patients.

Hemiparetic stroke patients in the transition to the chronic phase (n=10) will train activities of daily living (e.g., following predefined paths) with robotic support in immersive VR. To modulate the level of embodiment during the motor task, the patients will perform the activity of daily living with an avatar perceived from first- versus third-person perspective and with a symbolic representation (e.g., a cursor in the shape of a hand). We will record behavioural and neurophysiological (EEG) signatures of motor learning during training in VR. Body ownership will be assessed subjectively with established questionnaires. We expect that embodiment modulates motor brain networks engaged during motor learning and that motor learning is significantly increased when training with a higher (first-person perspective) versus lower (third-person perspective/symbolic) embodied avatar.

Together, this study will provide new insights into the neural correlates and behavioural benefits of embodying virtual limbs during robotic motor training and may open new perspectives for the neurorehabilitation of stroke patients.

Group 5 - Creativity, Neglect, Sensor-driven Assessment and Neuroprotection

Abstracts for selected Symposia
Keywords: Sleep, EEG, Creativity

Can creativity in healthy young subjects be boosted by napping? – Pilot

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Most likely, all of us experienced the refreshing effect of a nap. But could a nap boost our cognitive performance? Nap, just as a whole night sleep, can consist of four different stages, i.e., falling asleep phase (N1), light sleep (N2), deep sleep (N3) and rapid eye movement sleep (REM). Several previous studies found benefits of napping for basic cognitive functions (e.g., reaction times). However, more complex cognitive functions such as creativity have only sparsely been investigated.

A noteworthy distinction of creativity is between convergent and divergent thinking. While in convergent thinking a problem has only one optimal solution, in divergent thinking a plurality of solutions can be found. Previous results showed that REM during nap boosts convergent thinking (Cai et al., 2009).

The aim of the present pilot is to extend this line of research by investigating whether REM and non-REM during nap affect convergent and divergent thinking. To this end 40 healthy young subjects will perform a baseline measurement for creativity. After a wash-out period, subjects will either take a 60-minutes nap or a quiet rest, followed by a second creativity test.

We expect to see larger improvements in the creativity test battery in the nap condition compared to the quiet rest condition. Furthermore, we anticipate a positive correlation between REM and non-REM with convergent and divergent thinking, respectively. This study should provide insights into the correlation between sleep and creativity and whether a nap can be used as an intervention in improving creativity.

An item sorting heuristic to derive equivalent parallel test versions from a multivariate item pool

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Parallel test versions require a comparable degree of difficulty and must capture the same characteristics using different items. This can be challenging when dealing with multivariate items, which are for example very common in language or image data.

We propose a heuristic to identify and select similar multivariate items for the generation of equivalent parallel test versions. This heuristic includes: 1. inspection of correlations between variables; 2. identification of outlying items; 3. application of principal component analysis (PCA) as a dimension reduction method; 4. plotting of the first two principal components (PC) and grouping of the displayed items; 5. assigning of the items to parallel test versions; and, 6. checking the resulting test versions for multivariate equivalence, parallelism, reliability, and internal consistency.

To illustrate the proposed heuristic, we applied it on the items of a picture naming test. From a pool of 116 items, four parallel test versions were derived, each containing 20 items.

We found that our heuristic helps to generate parallel test versions that meet the requirements of classical test theory, while simultaneously taking several variables into account.

Aiming for more objectivity in creativity assessment - transcranial Random Noise Stimulation (tRNS) and machine learning applied in a verbal divergent thinking task

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Divergent thinking (DT) refers to an ability to produce multiple ideas to a given topic or various solutions to a given problem. Previous studies indicated that transcranial brain stimulation can improve performance in DT tasks. While the dorsolateral prefrontal cortex (DLPFC) is typically associated with executive functions, it has also been linked to idea selection. Here, we will apply tRNS to the DLPFC and evaluate the output in DT tasks by means of a custom-made algorithm providing a more objective and quantitative measure of semantic distances in participants' performances.

To this end, we will measure 40 healthy adults who will participate in two tRNS sessions (i.e., active and sham) that will be separated by a one-week interval. During 20 minutes of tRNS stimulation participants will perform a DT test battery. Participants' performance will be evaluated in terms of fluency (number of produced ideas), flexibility (semantic distances between ideas) and frequency-based originality (statistical infrequency of ideas). An algorithm will be developed that builds a model of semantic distances between the generated words using word embeddings. Subsequently, semantic distances between the generated ideas will be quantitatively measured.

The developed algorithm is expected to contribute to creativity research as it shall provide a more detailed and a more objective measure to assess the output of DT tasks. As such, this improved DT measure shall demonstrate to which extent the DLPFC is involved in DT tasks. Finally, given that models that are based on objective measures benefit from increased prediction accuracy, this more sensitive measure is expected to facilitate prediction of the post-stimulation improvement in the performance in DT tasks.

Keywords: Right-hemispheric stroke, Neglect; Video-oculography, Sensitivity, Test-retest-reliability

Eye know about your neglect: Eyetracking during free visual exploration (FVE) is sensitive and reliable to detect neglect

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Neglect after stroke is most accurately diagnosed by a systematic observations during daily living e.g. using the Catherine Bergego Scale (CBS). However, the CBS is often omitted in clinical settings due to its time-consuming procedure. Thus, with the present studies, we aimed to investigate if video-oculography during free visual exploration (FVE), which can be performed in few minutes, is sensitive and reliable to detect neglect.

In a **first study**, we aimed to investigate if FVE (i.e. mean gaze position on the horizontal axis) is sensitive to detect neglect in daily living and compare its sensitivity to conventional neuropsychological paper-pencil tests (i.e. Random Shape Cancellation, Line Bisection, Two-Part Picture, Bells, Star Cancellation, Letter Cancellation, Sensitive Neglect, and Five-Point). We identified 78 patients in our database with subacute right-hemispheric stroke, with and without neglect as diagnosed by the CBS and 40 age-matched healthy controls. FVE correctly identified neglect in 85% of patients and revealed an excellent AUC-value of .922 in ROC-analysis. Neuropsychological paper-pencil tests, considered alone or in combination, identified neglect significantly less often (21.74%-68.75%).

In a **second study**, we aimed to investigate the test-retest reliability of FVE in 23 neglect patients with subacute right-hemispheric stroke. The test-retest reliability was investigated between two different test sets (test sets A and B), and between repeated measures using the same test set C. The intra-class correlation coefficient (ICC) showed good to excellent reliability (ICC between test sets A and B =0.819; ICC for the repeated measures with test set C =0.964).

Taken together, FVE has a high sensitivity to diagnose neglect and is more sensitive than conventional neuropsychological paper-pencil tests. Furthermore, FVE shows good to excellent reliability. FVE can therefore be recommended for the longitudinal assessments of patients' neglect severity during treatment trials as well as a fast and accurate screening tool in the clinical setting, e.g. stroke units.

Abstracts for selected Symposia

Keywords: Neglect; Alerting; Insula; Inferior Frontal Gyrus (IFG)

A hub between ventral and dorsal visual attention systems: anterior insula and inferior frontal gyrus

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The link between spatial and non-spatial attentional aspects in patients with hemispatial neglect is well known on the clinical level: a temporary increase in alerting can transitorily help neglect patients to allocate attention towards the contralesional side. In influential models of attention, this phenomenon is postulated to rely on an interaction between ventral and dorsal cortical networks, subtending respectively non-spatial and spatial attentional aspects. However, the exact neural underpinnings of the interactions between these two networks are still poorly understood.

In this study, we applied non-spatial, auditory warning tones and measured the reaction to visual stimuli in 80 right-hemispheric patients with subacute stroke (40 women; age range: 24-96), with and without hemispatial neglect. In neglect patients, a warning tone, enhancing activity within the ventral attentional "alerting" network, could boost the reaction of the dorsal attention network to a visual stimulus up to the level of patients without neglect. Critically, using lesion-symptom mapping analyses, we show that this effect significantly depends on the integrity of the right anterior insula and adjacent inferior frontal gyrus.

We propose that the right anterior insula and inferior frontal gyrus are a critical hub through which the ventral attentional network can "alert" and increase the efficiency of the activity of the dorsal attentional network.

Abstracts for selected Symposia

Keywords: fMRI, TMS, sense of agency, motor control, functional neurological disorders

Modulation of the sense of agency in functional neurological disorders using non-invasive brain stimulation. A multimodal fMRI-TMS study

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Patients affected by functional neurological disorders (FND) experience neurological symptoms in the absence of lesions of the nervous system. These symptoms have been related to an abnormal sense of agency (SoA), the sense of control over voluntary actions. Interestingly, FND patients also show abnormal activity in the right temporo-parietal junction (rTPJ), a brain area involved in agency processing. In this study we tested whether transcranial magnetic stimulation (TMS) over the rTPJ modulates the SoA in FND patients and healthy controls (HC). First, we engaged 23 FND patients and 20 HC in a motor task designed to target the SoA during fMRI, and studied the activity of the rTPJ in the two groups. Second, we applied TMS in both groups in a sham-controlled, cross-over trial with excitatory, inhibitory, or sham stimulation. Our results showed that the rTPJ of FND patients was abnormally active, compared to HC. Inhibitory TMS over that area decreases the the SoA in HC, whereas it improved it in FND patients. We found evidence that, by restoring normal cortical activity in the rTPJ of FND patients, we improved the SoA. Our study opens to potential rehabilitation strategies for FND using non-invasive brain stimulation.

Abstracts for selected Symposia

Keywords: stroke, aphasia, nonverbal cognition, functional communication, voxel-based correlational methodology

The verbal, nonverbal and structural bases of functional communication abilities in aphasia

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The ability to communicate after stroke is crucial for the person involved and the people around them. Accordingly, assessment of functional communication is increasingly used in large-scale randomized controlled trials. Despite the importance of functional communication abilities to everyday life and their centrality to the measured efficacy of aphasia interventions, little is known about how commonly-used measures of functional communication relate to each other, whether they capture and grade the full range of patients' remaining communication skills and how these abilities relate to the patients' verbal and nonverbal impairments and to their lesions. Going beyond language-only factors is essential given that nonverbal abilities can play a crucial role in an individual's ability to communicate effectively. The current study, based on a sample of patients with chronic post-stroke aphasia, addressed these important, open questions. The investigation combined data from three established measures of functional communication with a thorough assessment of verbal and nonverbal cognition as well as structural neuroimaging. The key findings included: (a) due to floor or ceiling effects, the full range of patients' functional communication abilities was not captured by a single assessment alone, limiting the utility of adopting individual tests as outcome measures in randomized controlled trials; (b) phonological abilities were most strongly related to all measures of functional communication; and (c) nonverbal cognition was particularly crucial when language production was relatively impaired and other modes of communication were allowed, when patients rated their own communication abilities, and when carers rated patients' basic communication abilities. Finally, lesion analyses showed partially overlapping clusters in language regions for the functional communication tests. Moreover, mirroring the findings from the regression analyses, additional regions previously associated with nonverbal cognition emerged for the Scenario Test and for the Patient Communication Outcome after Stroke rating scale. In conclusion, our findings elucidated the cognitive and neural bases of functional communication abilities, which may inform future clinical practice regarding assessments and therapy. In particular, it is necessary to use more than one measure to capture the full range and multifaceted nature of patients' functional communication abilities and a therapeutic focus on nonverbal cognition might be beneficial.

Abstracts for selected Symposia

Keywords: contacless gait analysis, scanning rangefinders, Parkinson, telemedicine

Contactless Detection of Gait and Gait Abnormalities

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Background: In Switzerland, more than 15'000 people suffer from Parkinson's disease (PD). Gait disturbances are a classical symptom of the disease and are an important disabling factor for PD patients. The main gait disturbance results from bradykinesia and is characterized by a reduced step length and shuffling gait. Bradykinesia symptoms can be alleviated using a drug-based medical treatment. However, the effect of the treatment fluctuates through the day. To evaluate these fluctuations, as well as to quantify gait symptoms in general, gait tracking systems can be used. Most gait tracking systems available today require either to wear sensors or markers on the body, or to step on a specific surface equipped with sensors in a clinical setup.

Aim: We propose a compact and contactless gait tracking solution based on 2D scanning rangefinders that can readily be integrated in the patient's home.

Methods: Scanning rangefinders are placed at 25cm from the ground to track people's lower legs. Data processing can be divided into 4 main steps. The first step consists of removing static background information. The second step consists of identifying clusters of points corresponding to human legs. The third step consist of tracking the leg candidates across several frames. The fourth step consists of extracting the leg velocity to estimate the gait parameters.

We have measured the gait of 27 healthy young controls following a protocol including both controlled and uncontrolled gait. To evaluate the results of the proposed system, we have used both a gait-mat and a wearable gait sensor as gold-standards. All measurements were performed at the Neurotec Loft, a home-like experimental environment located at the SITEM in Bern.

Preliminary results: Relevant gait parameters such as step length, stride length or cadence can successfully be extracted from scanning rangefinder data.

Conclusion: 2D scanning rangefinders are a promising solution to track gait parameters in the patient's home. Their ability for contactless measurement of gait, as well as their limited size compared to other gait tracking systems on the market, make them well-suited for home integration.

Abstracts for selected Symposia

Keywords: Instrumented Apartment, Sensors, Behavioural and neurological disorders, Activities of daily living

The Neurotec Loft: An Instrumented Apartment to Monitor Human Behaviour and How Neurological Disorders Influence Daily Living

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Introduction: The NeuroTec Loft is an instrumented apartment located at the Sitem-Inselspital in Bern. The modern 3.5 room apartment has an open kitchen-living space, a bedroom, a toilet and a storage room. The apartment is designed and equipped with sensors to unobtrusive asses and monitor human behaviour and how neurological disorders (e.g. parkinson, multiple sclerosis, stroke, epilepsy, sleep disorders) influence daily life over a prolonged time. The goal of the NeuroTec Loft is to advance the quality and to enhance the cost-efficiency of healthcare.

Method: In order not to disturb patients and healthy subjects and thus to foster natural behaviour similar to living at home, the monitoring is primarily based on contact less sensors. In the open kitchen-living space, a high-resolution patient tracking system is installed (e.g. motion tracking and lidar). In the bedroom different sensor systems to measure physiological parameters and movement during sleep are installed (e.g. radar, infrared camera, ballistocardiograph, pressure mat). In addition, there is the possibility to assess sleep disorders by mobile polysomnography. To assess activities of daily living all doors and cupboards are equipped with sensors to measure if they are open or closed, furthermore power plugs, switches and water supply, environmental parameters (e.g. temperature, humidity, brightness) are monitored.

Results: The advantages of testing patients or healthy subjects in the NeuroTec Loft are that more detailed recordings can be performed. Furthermore, the NeuroTec Loft allows to have a standardized environment and thus the comparison between patients or healthy subjects. Currently, the sensor system is validated in healthy subjects, whereas studies with patients will start at the beginning of 2021 (e.g. the investigation how deep brain stimulation influences non motor symptoms or the investigation of performance of activities of daily living in patients after stroke or traumatic brain injury).

Conclusion: Overall, the NeuroTec Loft has a great potential to advance science in terms of human behavioural and neurological disorders in a home like environment and thus to address problems and increase quality of life of our aging society and patients with neurologic disorders.

Abstracts for selected Symposia

Keywords: visit detection, digital biomarker, older adults, late-life depression, pervasive computing

A Sensor-Driven Visit Detection System in Older Adults' Homes and its Potential to Extract a Marker for Late-Life Depression

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Background

Modern sensor technology is increasingly used with older adults to not only provide additional safety but also to monitor health status, often by means of sensor derived digital biomarkers. Social isolation is a known risk factor for late-life depression and a potential component of it is the lack of home visits. Therefore, home visits could serve as a digital biomarker for social isolation and late-life depression. Late-life depression is a common mental and emotional disorder in the growing population of older adults. The disorder, if untreated, can significantly decrease quality of life and, among other effects, does lead to increased mortality. Late-life depression often goes undiagnosed due to associated stigma and the wrong assumption that it is a normal part of ageing.

Objective

In this work we aim to evaluate different statistical learning strategies to build a robust visit detection system, that generalizes well to new apartments of community-dwelling older adults – which may differ largely in layout, sensor placement and size, compared to apartments found in the annotated training dataset.

Methods

1714 annotated visits, stemming from 15 (age = 86 ± 72 SD, sex = 54% female) community-dwelling and alone living older adults, were used to develop a self-learning derived domain adaptation approach.

Results

We found that by using a semi-supervised domain adaptation strategy, a robust system to extract home visit information can be built (ROC AUC=0.779). We further showed that the resulting visit information correlates well with the common Geriatric Depression Scale screening tool (= -.665; p = .026), providing further support for the idea of utilizing the extracted information as a potential digital biomarker to monitor risk of late-life depression.

Conclusion

We built a semi-supervised domain adaptation based visit detection system that allows to extract a visit score which was found to be significantly associated with late-life depression and could thus act as a digital biomarker for the same.