Basic Research Animal Abstracts:

Neural circuits for emotional conflicts and decision making in the ventral CA1 hippocampus

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The ventral part of the hippocampus is a key brain structure involved in a large-scale network mediating anxiety. However, its role in arbitrating approach-avoidance behaviour during emotional conflicts is still unclear. To test for an involvement of the ventral CA1 hippocampus (vCA1 HC) in decision-making processes during emotional conflicts, I have characterized the neural activity of vCA1 HC cells in mice facing emotional conflicts using novel behavioural tasks combined with single-unit recordings.

Our preliminary results reveal a scaling in neural activity in the overall population recorded and a remapping of firing-rate spatial fields during anxiogenic situations. These results were selective for the conflict level the animals faced and were novelty-independent.

Moreover, an important target of the vCA1 HC thought to be crucial for the coordination of decision-making behaviour is the medial prefrontal cortex (mPFC). The neural activity of the subgroup of vCA1 HC to mPFC projection cells exhibited decision-making related activity similar to the overall population recorded and their optogenetic inhibition performed at the axon terminals level influenced decision-making processes during emotion conflicts.

Taken together, these results further confirm the strong involvement of the vCA1 HC in anxiogenic situations and support the hypothesis that pyramidal cell assemblies within the vCA1 HC represent different emotional conflicts during decision-making processes.

Keywords: ventral hippocampus, decision-making, emotional conflicts, medial prefrontal cortex, network activity

Spinal cord grey matter demyelination in myelin oligodendrocyte glycoprotein-IgG and aquaporin 4-IgG augmented experimental autoimmune encephalomyelitis

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Introduction
Widespread focal demyelination is a common hallmark of inflammatory central nervous system (CNS) disorders such as multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG)-IgG associated disorder (MOGAD). Although demyelination is often associated with myelin-rich white matter lesions, grey matter is not spared. In experimental autoimmune encephalomyelitis (EAE), an animal model for demyelinating CNS inflammation, investigation of grey matter demyelination (GMD) is scarce.

Methods
Active MOG_{35-55} EAE was induced in C57BL/6Jrj mice and a monoclonal MOG-IgG (8-18C5, murine, n=10), AQP4-IgG (rAb-53, human, n=9) or isotype matched control IgG (Iso-IgG, human, n=6) was administered 10 days post immunization (dpi). Control animals were sham immunized and received Iso-IgG 10 dpi (n=9). Demyelination of the spinal cord white and grey matter was visualized 28 dpi by Luxol fast blue and myelin basic protein (MBP) staining. Extent of ventrolateral white matter lesions was assessed and deep lesions extending

from meninges to grey matter border were further analysed for potential GMD. GMD was defined as loss of MBP-positive fibre integrity and deposition of MBP-positive granules in the ventral horn.

Results

Lesion localisation significantly differed between the antibody-augmented groups ($p<0.0001$). MOG-IgG augmented EAE animals (mean clinical score ± standard error 5.5±0.42 on a 10-point scale) demonstrated more deep ventrolateral (VL) lesions than AQP4-IgG augmented (3.0±0.39) or Iso-IgG EAE animals (2.9±0.45) with a frequency of 52%, 13% and 21% of all VL lesions extending from meninges to grey matter border ($p<0.01$). Of these deep lesions, 56% (MOG-IgG EAE), 52% (AQP4-IgG EAE) and 29% (Iso-IgG EAE) were associated with GMD in the ventral horn ($p=0.40$). Loss of MBP-positive fibre integrity and deposition of MBP-positive granules was detected in diseased animals but not in controls.

Conclusions

Even though deep VL demyelinating white matter lesions were more frequent in MOG-IgG augmented EAE animals compared to AQP4-IgG or Iso-IgG EAE, the proportion of these lesions with associated GMD was similar in all groups. Thus, ventral horn GMD may be linked to VL white matter lesion depth. Interestingly, antibody specificity may influence lesion localisation in the EAE model.

Keywords: NMOSD, MOGAD, experimental autoimmune encephalomyelitis, grey matter demyelination

Investigation of vitamin D signaling via the glucocorticosteroid receptor

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Introduction/Aim

Several evidence suggest a beneficial effect of vitamin D (VD) on multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). It has already been shown that VD administration reduces EAE severity in vivo. Preliminary data from our group demonstrated that the beneficial effects of VD on EAE observed in wild type (WT) mice were lost in T cell specific glucocorticoid receptor (GR)-deficient mice suggesting a possible role of the GR in VD efficacy. The aim of this study is to determine the contribution of the GR in VD-induced effects.

Methods

Myelin oligodendrocyte glycoprotein (MOG35-55) EAE was induced in female C57BL/6JRj WT- and T cell specific GR-deficient mice. Four different concentrations of calcitriol (1-1000ng), the active form of VD, were given orally after disease onset for three consecutive days. GR mRNA expression was measured ex vivo by real-time polymerase chain reaction in CD3+ T cells after calcitriol treatment. T cell apoptosis and T regulatory (Treg) differentiation were analyzed in vitro by flow cytometry with CD3+ T cells from both WT and T cell specific GR-deficient mice.

Results

Three days of calcitriol treatment (from 1ng/day to 100ng/day) significantly reduced EAE severity in WT mice whereas no beneficial effect was observed in T cell specific GR-deficient mice. In contrast, calcitriol treatment at a concentration of 1000ng/day worsened the disease in both genotypes. In vitro results showed that calcitriol treatment significantly promoted apoptosis and Treg differentiation of CD3+ T cells from WT mice whereas these effects were abolished in CD3+ T cells from T cell specific GR-deficient mice, corroborating in vivo results. Finally, calcitriol increased GR mRNA expression in CD3+ T cells of WT but not of T cell specific GR-deficient mice ex vivo.

Conclusions

Preliminary results showed that the GR appears to be required for proper calcitriol effects. We also observed that a too high concentration of calcitriol has a detrimental role on EAE. Further investigations are needed to determine the exact role of the GR in calcitriol signaling and to identify the mechanisms underlying the complex dose-response relationship of calcitriol in EAE.

Glial involvement in the development of a fibrotic scar after laser-induced retinal degeneration

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Purpose: Degeneration in the human retina leads to visible remodeling processes, whereby the typical retinal layer structure gets lost. During the process, glial cells change morphology and establish a glial scar to contain degenerated tissue and to support remodeling of the retinal extracellular matrix (ECM). Fibrosis can develop in the course of the ensuing degeneration. So far, the mechanism responsible for limiting the regenerative capacity of mammalian glial cells nor the process of the retinal wound healing are well known. With that, there is no successful treatment imaginable.

Methods: C57BL/6J mice underwent laser photocoagulation to induce retinal fibrosis. Autofluorescence was employed to visualize the extent of laser damage, whereas the lesion size was quantified with optical coherence tomography (OCT) measurements. Hematoxylin and eosin staining (H&E) was performed on paraffin sections to follow degenerative changes over time. Additionally, confocal microscopy of paraffin sections stained for gliotic markers glutamine synthetase (GS), glial fibrillary acidic protein (GFAP) and fibrotic markers such as fibronectin or type 1, 3 and 4 collagen after laser injury and during upcoming fibrosis from 3 h post injury (pi) up to day 49 pi.

Results: From day 1 to day 49 after laser injury the leakage observed in the fluorescence angiography decreased whereas the subretinal scar in the OCT images increased. Furthermore, the expression of GFAP-positive, activated glial cells did not decrease over time. However, the expression of the different collagens in the lesion area increased reciprocally, whereas the fibronectin content decreased.

Conclusions: During retinal degeneration, collagens are seen to replace fibronectin in the damaged area. The results also indicate that glial cells are involved in the development of a fibrotic scar and thereby hamper the regeneration in the retinal tissue decisively.

Keywords: Degeneration, Glia, ECM, Fibrosis

A Dance between the Emotions and the Physicality of Pain: Differential Modulation of Behavioral Responses to Pain in Sleep and Wake depends on the Interplay between the Somatosensory Cortex and the Anterior Cingulate Cortex

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The experience of pain consists of both emotions and physical sensations. These receive the name of affective motivational and sensory-discriminative components and are processed by the lateral and the medial pain pathway, respectively. These pathways rely on different spino-thalamo-cortical pathways that terminate in either the anterior cingulate cortex (ACC), which processes the affective-motivational aspect, or the primary somatosensory cortex (S1), in charge of sensory discrimination. Nevertheless, while we know how pain is processed during wake, it remains to be elucidated how pain is processed in sleep.

To reveal differences of pain processing in wake and sleep, we performed multisite bi-hemispheric intracranial tetrode recordings in the ACC and the hind paw S1 (S1HL) of mice. Then, mice received painful mechanical stimuli at the plantar surface of the hind paws in wake and sleep.

Here we show for the first time how painful mechanical stimuli do reach the cognitive cortex (ACC) and the sensory cortex (S1HL) in natural sleep, indicating the emotional component of painful stimuli is also processed during sleep. We also observe that the type of the behavioral reactions subsequent to the stimuli depend on the interplay between S1HL and ACC. For instance, heightened gamma (30 – 100 Hz) power in the S1HL at the time of the stimulation predicts the presence of behavioral response in wake but not sleep. Interestingly, ACC neural activity before the stimulation does not predict the behavioral reaction in wake, but in sleep. During sleep, high theta (5 – 9 Hz), sigma (30-45 Hz) and gamma power in the ACC predicts the stimulus will not result in an arousal. Summarizing, these results indicate that the emotional component of pain is processed during sleep and, together with the sensory-discriminative processing, it shapes the behavioral reaction.

Seen these findings, we hypothesize that the continuous influx of pain information that gets processed during sleep in early stages of chronic pain could be the trigger of the thalamo-cortical dysrhythmia observed in patients with chronic pain. Therefore, we are currently testing this hypothesis using a mouse model of chronic pain.

Keywords: sleep, pain, somatosensation, LFP

Characterization of Layer 5 Pyramidal Neurons of the Anterior Cingulate Cortex in Inflammatory Pain

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The neural network activated by noxious stimuli involves several brain regions. Of primary interest is the contribution of the anterior cingulate cortex (ACC) in processing the affective component of pain. The ACC is consistently activated by noxious stimuli and it has been shown to play a role in determining the subjective experience of pain by integrating cognitive, emotional, and motivational component.

Here we are testing the hypothesis that specific neuronal populations within the ACC undergo different plastic changes in response to inflammatory persistent and stimulus-evoked pain.

To dissect the functional pain responsive neurons in the ACC we used a rodent inflammatory pain model, by injecting the Complete Freund's Adjuvant (CFA) in the hindpaw of male mice. A group of mice injected with CFA was considered to be in persistent pain given solely by the injection. Another group of mice injected with CFA has additionally received a daily noxious stimulation via pinprick needle for a week as a model of stimulus-evoked pain. To investigate how the peripheral injury changes the general neuronal activity we performed whole-cell patch-clamp recording in brain slices.

All CFA mice developed mechanical and thermal hyperalgesia, as measured with the electronic von Frey and the thermal plate, as compared to the saline mice. At the cellular level, we observed changes in intrinsic electrical properties between CFA and saline mice in both acute (d1) and persistent phase of inflammation (d7). Data show that plasticity in the ACC is observed in CFA mice at d1 with a lower excitability of the L5 subcortical pyramidal neurons; after a week of ongoing inflammation, only mice that received a daily pinprick stimulus showed increased excitability of the neurons. Intrinsic electrical properties differ in input resistance, rheobase threshold, firing rate and action potential features.

Persistent and stimulus-evoked pain can influence differently the activity of the ACC. Although, the function of this plastic adaptation of pyramidal neurons in L5 is not known yet.

Keywords: Pain, Anterior Cingulate Cortex, Inflammation, Stimulus-evoked Pain

Rho-kinase involvement in an animal model of subretinal fibrosis

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Background: Age-related macular degeneration (AMD) is the leading cause of adult vision loss in the developed countries. Subretinal fibrosis can evolve in the course of neovascular AMD. Rho-associated, coiled-coil-containing protein kinases are involved in cytoskeletal rearrangement, contractility, angiogenesis and inflammation. Rho kinases have multiple functions, including the maintenance of cell viability and morphology, in part by regulating stress fibres and focal adhesions[1,2]. Rho-kinase inhibitors are compounds that target rho kinase (ROCK) and inhibit the ROCK pathway[3]. Rock has been implicated in fibrosis formation[4].**Purpose:** Investigate the impact of the ROCK inhibitor fasudil on subretinal fibrosis after CNV.**Methods:**To induce CNV-related fibrosis, C57BL/6J mice were anaesthetized. Using a 532-nm laser, a slit-lamp delivery system, six spots were placed in each eye. The mice were then treated intraperitoneally with fasudil 20 mg/kg every day from day 35 after laser injury for two weeks. The volume of CNV and fibrosis was quantified with optical coherence tomography (OCT) measurements and with choroidal flat mounts every week after laser injury. Additionally, we performed autofluorescence and fluorescence angiography at every time point to document CNV and

fibrosis changes over time.**Results:** The leakage in the fluorescence angiography decreased and the subretinal fibrosis in the OCT images increased over the investigated time.The pan-ROCK inhibitor, Fasudil, substantially reduced subretinal fibrosis in vivo. With fasudil fibrosis markers, such as collagen1 and α-SMA, in the subretinal fibrosis lesions decreased significantly compared to the control group (vehicle-treated mice) at day 49 after laser injury.**Conclusions:** The pan-ROCK inhibitor fasudil has therapeutic potential for the treatment of subretinal fibrosis in neovascular AMD.**References:**1. Leung T, Chen XQ, Manser E, Lim L (October 1996). "The p160 RhoA-binding kinase ROK alpha is a member of a kinase family and is involved in the reorganization of the cytoskeleton". Molecular and Cellular Biology. 16 (10): 5313–27.2. Liao JK, Seto M, Noma K (July 2007). "Rho kinase (ROCK) inhibitors".Journal of Cardiovascular Pharmacology. 50 (1): 17–24.3. Liao, James K.; Seto, Minoru; Noma, Kensuke (July 2007). "Rho Kinase (ROCK) Inhibitors". Journal of Cardiovascular Pharmacology. 50 (1): 17–24.4. Wang SK, Chang RT (2014). "An emerging treatment option for glaucoma: Rho kinase inhibitors". Clinical Ophthalmology. 8: 883–90.

Keywords: Rho-kinase, Rock, retinal, subretinal fibrosis, AMD, CNV, ROCK inhibitor, fasudil

ON-bipolar cell targeted optogenetic gene therapy in light of retinal degeneration: Functional evaluation using multi-electrode arrays

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Retinitis pigmentosa (RP) represents a heterogeneous group of genetic disorders responsible for massive photoreceptor degeneration and subsequent gradual loss of vision in patients. Such event also affects inner neural layers resulting in cellular disorganization, aberrant expression of proteins or pathological neuronal activity. Despite these changes, there is still possibility of intervention and restoration of light sensitivity and eventually vision in blind retinas. Such intervention is feasible using methods including stem cell therapy, synthetic photoswitchable ligands, electronic prostheses or optogenetics. The latter combines most of the advantages of other mentioned approaches – cell specificity, direct and temporally regulated light activation, long-lasting effectiveness, and simple and safe ambulant delivery of the therapy.

Opto-mGluR6 is a designer protein that couples light sensitivity of melanopsin with intracellular signalling of the metabotropic glutamate receptor 6 (mGluR6). As mGluR6 is the direct transmitter of the light signalling cascade from rods and cones to ON-bipolar cells, Opto-mGluR6 represents a natural candidate for successful vision restoration in blindness. Employing a mouse model of RP treated with AAV vectors carrying Opto-mGluR6 under a highly specific synthetic ON-bipolar cell promoter, the Kleinlogel Group was able to achieve robust reactivation of visual signalling.

Here I present my progress in different areas tightly bound by the common goal of the lab: quantifying restored visual output of the retina treated with Opto-mGluR6 based optogenetic gene therapy. Insights gained from this project will shine light on the quality of potentially restored vision by optogenetic manipulation of bipolar cells and elucidate retinal network adaptations during degeneration.

Keywords: optogenetic gene therapy, Opto-GPCRs, vision restoration, multi-electrode array recordings, rd1 mouse line

Retinal Interneurons play a key role in heath, disease and therapy: not just "connectors".

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In the last two years of the pandemic we have been experiencing a disconnection from the outside world. Visual disconnection from the sensory world around us, is exactly what 4% of the population of the planet, suffering from blindness, experiences daily basis.

Retina consist of several specialized cell types. The retina interneurons, known as bipolar cells, are not just the connectors between photoreceptors (light sensitive cells of the retina) and ganglion cells (final retinal output),

but they play a key role in the modification and transmission of a light activated signal into the inner retina layers.

In Retinitis Pigmentosa the death of the photoreceptors leaves behind a light insensitive retina.

Luckily retina interneurons are able to survive and can be used as cell target for genetic therapy. Thanks to specific genetic tools Scientists today are able to modulate and transform a specific cell type in other cell type: in our prospective turning interneurons in replacement photoreceptors with an optogenetic therapeutic approach for the treatment of blindness. The Optogenetic approach is promising and it gave so far realistic results. However, retina degeneration brings to alterations of the retinal network: lacking of cell dendrites, alteration in protein expression, protein mislocalization. These modifications can of course impact in a bad way this synthetically achieved vision restoration. For this reason by characterizing retinal interneurons in healthy and disease determining their electrophysiological, molecular and morphological features, we aim at optimizing restorative approaches and improving functional output. In our study, we reported with molecular, histochemical and electrophysiological techniques the impairment of a potassium channel in retinal interneurons of degenerated retina. In combination with bipolar cell transcriptomics we hope to in the future be able to complement retinal interneurons in the degenerated retina with proteins that re-establish natural signalling.

Keywords: interneurons, retina, degeneration, ion channels, genetics

Optical mini-stroke of thalamic networks impairs sleep stability, oscillatory topography and cognition.

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Modelling stroke in animals remains a challenge for translational research, especially for the infraction of small *subcortical* arteries. Using combined fibre optics and photothrombosis technologies, we developed a novel model of optically-induced infarcts (Opto-STROKE). Combining our model with electrophysiological recordings in freely-behaving mice, we studied early and late consequent patho-physiological changes in the dynamics of sleep-wake circuits and cognitive performance. Here, focusing on inducing Opto-STROKE lesions in the intralaminar thalamus (IL), which in humans cause severe impairments of arousal, cognition, and affective symptoms, our model recapitulated important deficits on sleep disorders presented in humans including arousal instability, concurrent to an augmented slow-wave activity and a reduction gamma power bands during wakefulness. Moreover, during NREM sleep, spindle density was decreased and topographically shifted to frontal cortices when compared to control animals. Remarkably, gamma power and spindle density were correlated with decreased pain threshold and impaired prefrontal cortex- dependent working memory in Opto-STROKE mice relative to controls. Collectively, our combined method influences both anatomical and functional outcomes of the classical stroke procedures and offers new insights on the fundamental role of the media thalamus as a hub for the regulation of both sleep-wake architecture and cognition.

Keywords: Stroke model, sleep, thalamic networks

Principles of Nociception in the Anterior Cingulate Cortex

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The perception of pain, as a complex sensory and emotional/affective experience, arises from distributed brain activity upon nociceptive stimulation. However, these areas are not selective for pain. Thus, how each territory distinguishes nociception from other aversive and salient stimuli remains elusive. Additionally, the change of activity pattern within regions upon sensory stimulation and its consequential relationship in chronic pain have not been attained. Using time-lapsed *in vivo* calcium imaging in freely moving and slightly anaesthetized mice,

we investigated the principles of nociceptive coding in the anterior cingulate cortex (ACC), a region essential for the emotional processing of pain. The overall neuronal activity allowed efficient discrimination in the sensory space, despite a drift in single-neuron tuning over time. A subset of neurons coded for a generalized feature of the nociceptive experience, forming a dedicated high-threshold saliency-detection network. Chronic pain led to a dysfunctional discrimination of sensory events caused by an exacerbation of saliency-detection and an impairment of pattern separation and classification. These results provide a novel interpretation for pain processing in the normal and diseased brain.

Keywords: Chronic pain, nociception, neuronal activity, cingulate cortex, mice.

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. 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. 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.

Ambient temperature (Ta) manipulation as a novel technique to dis-sociate REM sleep and cataplexy in narcolepsy

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The lateral hypothalamic melanin-concentrating hormone (MCH) system is critical for maximizing REM sleep during thermoneutral ambient temperature (Ta) warming (Komagata et al., 2019). Given the role of the hypocretin (Hcrt) system in MCH inhibition, we hypothesized that Hcrt loss in narcolepsy may enhance REM expression or cataplexy during Ta warming. We thus investigated REM sleep expression as a function of Ta during both light (inactive) and dark (active) phases in wild-type (WT), MCH receptor 1 Knock-out (MCHR1-KO) and narcoleptic Hcrt-KO mice.
Mice were implanted for sleep-wake monitoring with additional video recording for cataplexy and actigraphy analyses. During the light or dark phase, mice underwent a Ta manipulation protocol that consists of using a combination of convection heater and indirect infrared heater lamp to have four bouts of rapid warming to reach the high end of mouse thermoneutral zone (TNZwarm), followed by passive cooling bouts with the Ta at the low end of mouse thermoneutral zone (TNZcool).
WT mice significantly increased REM sleep expression with Ta warming during the light phase, but not in the dark phase. As expected, MCHR1-KO mice did not respond to Ta warming during either light and dark phase. Unexpectedly, we found reversed circadian REM sleep responsiveness pattern to Ta warm-ing compared to WT mice, showing increased REM sleep only during the dark phase. Additionally, nar-coleptic mice significantly decreased cataplexy during Ta warming, revealing a dynamic dissociation of REM sleep and cataplexy. This

effect was amplified after the food-elicited cataplexy test (FECT). Taken together, these results suggest that Ta manipulation might be used to dissect neural mechanisms underlying REM sleep and cataplexy and it might be a novel technique to modulate their expression for clinical aims.

Comparison between CRISPR-mediated HITI and MITI for Opto-mGluR6 expression.

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Retinitis Pigmentosa (RP), an inherited form of retinal degeneration, is characterized by a progressive loss of rods and subsequent degeneration also of cones leading to blindness. However, the remaining neural part of the retina (bipolar and ganglion cells) remains anatomically and functionally intact for an extended time period. A possible treatment consists in rendering these remaining cells photosensitive using optogenetic tools like, for example, Opto-mGluR6, a chimeric protein of human origin developed in our lab. In previous studies, we have demonstrated that the AAV vector mediated expression of Opto-mGluR6 in ON bipolar cells (ON-BPC) can restore visual function in otherwise blind RP mouse models.

Classical gene addition still suffers of drawbacks such as specificity of expression, control of expression levels and promoter silencing. To overcome these issues, we are using two approaches based on the use of the CRISPR/Cas technology namely HITI (Homologous-Independent Target Integration, based on spCas9 or saCas9) and MITI (MIcro-homology Targeted Integration, based on Cpf1) to knock-in (KI) Opto-mGluR6 downstream to an ON-BPC specific promoter. This should lead to a specific and physiological level of expression of our construct.

After having selected the best performing sgRNA target sequences for each system, we confirmed, in vitro, the possibility of an efficient KI through both HITI and MITI. Next, we prepared dual AAV vectors for testing both HITI and MITI in vivo with the aim to express Opto-mGluR6 selectively in ON-BPC of C57Bl/6 mice.

Keywords: Gene therapy, Optogenetics

Paradoxical somato-dendritic decoupling supports cortical plasticity during REM sleep

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REM sleep is associated with the consolidation of emotional memories encoded by neuronal circuits from the limbic system and prefrontal cortex in mammals. Yet, the underlying neocortical circuits and synaptic mechanisms remain unclear. Here, we found that REM sleep is associated with a somato-dendritic decoupling in pyramidal neurons of the prefrontal cortex, using simultaneous 2-photon calcium imaging and electrophysiological recordings in sleeping mice. This decoupling reflects a shift in inhibitory balance between PV neurons-mediated somatic inhibition and VIP-mediated dendritic disinhibition, mostly driven by neurons from the mediodorsal thalamus. We further showed that REM-specific optogenetic suppression of dendritic activity led to a loss of danger versus safety discrimination during associative learning and a lack of synaptic plasticity, whereas optogenetic release of somatic inhibition resulted in enhanced discrimination and synaptic potentiation. In sum, somato-dendritic decoupling during REM sleep promotes opposite synaptic plasticity mechanisms that optimize future emotional response to behavioral stressors.

Understanding the function and role of inflammatory reactive astrocytes in acute perinatal white matter injury

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Acute perinatal 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, and defective oligodendrocyte maturation. Recent studies in the injured mature brain highlight the formation of diverse reactive astrocyte subtypes with contrasting roles after injury, some favoring brain repair and other «inflammatory» astrocytes contributing to neurodegeneration. The specific nature of astrocyte reactivity after WMI remains obscure. We know that these inflammatory astrocytes (iAs) are induced by activated microglia-derived IL-1α, TNF, and C1q and lead to myelination failure, an outcome characteristic of WMI. Given that iAs inhibit the maturation of myelinating cells, we hypothesize that iAs play a central role in WMI and may be an exciting therapeutic target for this disease. We report the results of experiments aimed to investigate the formation, function and therapeutic modulation of iAs in WMI.

iAs formation was analyzed across multiple rodent WMI models using a combination of hypoxic-ischemic and inflammatory insults. To confirm experimental WMI, myelin deficits were evaluated using immunohistochemistry for MBP. iAs formation was investigated through in situ hybridization (ISH) using a complement component 3 (C3)-specific probe. We further characterized astrocyte reactivity by performing microfluidic qRT-PCR analysis using a panel of known reactive astrocyte transcripts on mRNA isolated from primary astrocytes purified through immunopanning from injured and healthy brains. IL-1α/TNF/C1q knockout mice unable to generate iAs were used to investigate the necessity of iAs for WMI outcomes.

ISH demonstrates a significant increase of C3-positive iAs in subcortical white matter tracts across multiple rodent WMI models. Supporting this finding, qRT-PCR results suggest that purified astrocytes from injured brains exhibit a multi-gene inflammatory astrocyte signature at the transcriptome level. Ongoing experiments in mutant mice test whether iAs are central drivers of WMI pathogenesis.

Our experiments demonstrate the formation of iAs in multiple rodent WMI models, test these cells' ability to drive WMI outcomes, and work towards an in-depth characterization of astrocyte polarity in WMI. Guided by these results, we will evaluate the therapeutic potential of optimizing astrocyte polarization to improve WMI outcomes.

Keywords: reactive astrocytes, perinatal WMI, RNAscope, C3, IL-1α/TNF/C1q knockout mouse

Optogenetically disentangling the differential role of beta-adrenoceptor signalling

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Traditional optogenetic tools, including channelrhodpsin-2 (ChR2), are widely used to control membrane potential, however, these microbial opsins are depolarizing ion channels or hyperpolarizing ion pumps, and not G-protein coupled. Since biological systems are extensively modulated by G-protein coupled receptors (GPCRs), the interest in the development of novel optogenetic tools, such as light-activatable GPCRs (Opto-GPCRs), has grown exponentially. Engineered chimeric Opto-GPCRs, such as Opto-mGluR6 designed by the Kleinlogel lab to restore vision possess a light-sensitive extracellular opsin domain (melanopsin in Opto-mGluR6) and an intracellular domain of the particular target receptor (mGluR6 in Opto-mGluR6), mediating the respective G-protein signaling cascade in the target cell. Engineered chimeric Opto-GPCRs have been used to modulate cellular signaling pathways by light activation, and therefore provide a viable option to study biochemical signaling pathways with great spatio-temporal control.

GPCRs couple to diverse heterotrimeric G proteins, including Gs, Gi and Gq, which activate respective downstream signaling pathways. Previously, the intracellular loops two (ICL2) and three (ICL3), as well as the

proximal C-terminus (CT) have been shown to be structurally involved in G protein selectivity. Here, we designed and implemented chimeric Class A (beta-2-adrenoceptors) and Class C (mGluR6) Opto-GPCRs. Using live cell assays of GPCR coupling to functionally determine the G-protein specificity via second messenger imaging, we compared the involved regions in Class A and Class C GPCRs, as well as in Gi-, Gs-, and Gq-G protein activation.

Keywords: GPCRs, G proteins, Optogenetics

Probing cortical excitability and seizure resilience under GABAergic modulation

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Rationale:

Cortical excitability, defined as the variable response to a given cortical stimulation, is widely studied in neuroscience and epilepsy research, from slice experiments and in silico modeling work to clinical pharmacology in humans, but its relationship to seizure occurrences remains to be understood.

Recent modeling and experimental work suggested that changes in seizures resilience should be preceded by changes in cortical excitability. However, in-vivo validation of these concepts and their broader applicability to the non-epileptic brain are currently lacking.

Methods:

In this study, we quantified cortical excitability as the evoked local field potential responses to both single and paired pulses of in-vivo optogenetic stimulations in awake, freely-moving mice.

We also used train of optogenetic stimulation to induce hippocampal seizures and measured cortical resilience as the time of stimulation needed to elicit a seizure (time-to-seizure).

We then explored how these markers varied in the presence of GABAergic agonist (Diazepam (DZ)) and antagonist (Pentylenetetrazol (PTZ) and Picrotoxin (PTX)).

Results:

We found that evoked cortical response to single opto-pulse was reduced by 29.3% 95%CI [27.6-31.2] in presence of DZ and increased with GABAergic antagonist (5.1% [3.0-7.1] for PTZ and 9.3% [7.1-11.3] for PTX). GABAergic drugs also modulated cortical resilience with a 78.1% [54.5-113.0] increase in time-to-seizure in presence of Diazepam and a respectively 19.6% [3.0-10.8] and 10.6% [-4.0-18.5] decrease with PTZ and PTX, corroborating the changes observed in cortical excitability.

Conclusion:

In this study, using minute perturbations of ongoing activity, we probed and quantified varying degrees of cortical excitability, modulated bidirectionally by GABAergic drugs. We provide strong *in vivo* experimental evidence for a direct relevance of these markers of cortical excitability to assess resilience to perturbations and susceptibility to seizures, confirming previous in vitro and in silico work.

From a translational perspective, the ability to gauge cortical excitability over time with minimal perturbations may open the way to refined diagnostic and therapeutic approaches in chronic dynamical brain disorders such as epilepsy.

Keywords: Epilepsy, Seizure, Optogenetic

Aversion learning mediated by dopaminergic neurotransmission in the anterior cingulate cortex

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Synaptic plasticity is instrumental for cognitive functions. Moreover, cortical plasticity rules can be influenced by neuromodulatory inputs. The anterior cingulate cortex (ACC) is a brain region involved in error detection,

pain processing and aversive learning. The ACC is highly regulated by dopaminergic inputs. However, the relationship between synaptic plasticity and the role of dopamine in the ACC in the context of aversive learning has not been yet characterized.

Our results show that at L5 pyramidal neurons in the ACC, dopamine facilitates plasticity at electrically-evoked proximal synapses. Moreover, at distal synapses we show that pairing specific inputs from the contralateral ACC leads to synaptic depression, which is occluded in the presence of dopamine. Conversely, at proximal synapses, activation of contralateral inputs is devoid of synaptic plasticity, but is depressed by dopamine. This indicates that synaptic plasticity at ACC L5 pyramidal neurons is differentially modulated by dopamine depending on both dendritic synaptic location and presynaptic input.

Next, we investigated the role of the ACC in aversive learning in a place avoidance task. Our results suggest that inhibition of neuronal activity in the ACC leads to an impairment of aversive learning.

These results therefore indicate that dopaminergic neuromodulation can selectively differentiate specific inputs at different synaptic sites, potentially acting as a plasticity switch mechanism. Furthermore, we show that the ACC is important for aversive learning. Here we show a mechanism which could explain how the ACC computes the vast and often contradictory inputs it receives.

Keywords: Anterior cingulate cortex, Dopamine, Aversive learning, Spike timing dependent plasticity

The coordinating influence of thalamic nucleus reuniens on sleep oscilla- tions in cortical and hippocampal structures – relevance to memory con- solidation and sleep structure

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There is currently a substantial amount of neurophysiologic data showing temporal coupling of discrete EEG/LFP events in prefrontal cortex and hippocampus. More concretely, both delta waves and spindles in prefrontal cortex tend to co-occur with sharp-wave ripples in hippocampus. On a functional level, this phenomenon seems to be involved in memory consolidation.
However, to this day it is not known what mechanisms enable this synchrony. A possible solution might be found in the thalamus. The nucleus reuniens is a part of the median thalamus and has reciprocal anatomical connections to both prefrontal cortex and the hippocampal formation. Concretely, it sends axons to the deep layers of the prefrontal cortex and to str. Lacunosum moleculare of the CA1, while receiving input from the same layer of the cortex and from subiculum.
We show in our work a confirmation of the aforementioned anatomical findings and we show for the first time measures of connectivity between delta waves and spindles in nucleus reuniens and hippocampal ripples, while also confirming findings for prefrontal cortex and hippocampus. Attached to that, we additionally show the density of spindles and ripples over time as discrete events for hippocampus (ripples), nucleus reuniens and prefrontal cortex (spindles). Lastly, we can show that by optogenetically manipulating nucleus reuniens, we can have an influence on the coupling between cortex and hippocampus.
Furthermore, we show the behaviour of single neurons in nucleus reuniens in relation to hippocampal sharp-wave ripples.

Keywords: Neurooscillations, Optogenetics, Sleep physiology

Optogenetic Manipulation of the Thalamocortical Circuits of Pain

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Somatosensation and pain are essential, complex, and tightly regulated neurobiological processes. Specific pathways of the thalamocortical circuit partake in the processing of nociceptive information. The thalamus

relays the neural signals from the periphery to the cortices. More in detail, the lateral pain pathway transmits sensory-discriminative information from the Ventro-posterolateral nucleus of the thalamus (VPL) to the somatosensory cortex. While the medial pain pathway, from the mediodorsal thalamic nucleus (MD) to the anterior cingulate cortex (ACC), processes the emotions that accompany pain. However, the thalamocortical system is intricate and the precise functional contribution of its different elements in building the pain experience remains unclear.

Recent research in the lab, using intracranial tetrode recordings in the mouse, hints that the hind limb area of the somatosensory cortex (S1HL) and the ACC activity differently modulates the behavioral responses to painful stimuli in the hind paw. These two behavioral responses are withdrawal of the paw and awakening from NREM sleep. Interestingly, these two responses, do not seem dependent on one another.

Therefore, the aim of this study is to determine the contributions of the S1HL and ACC in the behavioral outcome of the stimuli. To do so, we will use optogenetic tools to modify the activity of these regions, at the time of the stimulation, to evaluate changes in the behavioral outcomes. Then, we will combine optogenetics with electroencephalogram recordings to evaluate changes in arousability.

These experiments are implemented in a larger study investigating by electrophysiological recordings and behavioural testing the interplay of pain processing and sleep in the mouse thalamocortical networks.

Keywords: Somatosensation, pain, optogenetics

The Potential Role of RTK MET Serine1014 Phosphorylation Site in the Development of Autism Spectrum Disorders

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Background. Receptor tyrosine kinase MET is an oncogene involved in multiple cellular functions. Besides, variants of the MET gene are enriched in patients with Autism Spectrum Disorder (ASD). ASD is an early-onset neurodevelopmental disorder, characterized by cognitive decline, impaired social communication, restrictive and stereotyped behavior. MET is one of the key players in synapse formation, maturation, and process outgrowth. Disrupted synapse formation is one of the ASD pathways. Within a phosphoproteomics study carried out by our group, a previously unreported phosphorylation site of serine 1016 (equivalent to mice serine 1014 (S1014)) of MET was identified. To functionally characterize this phosphosite, a knock-in mouse model lacking the phosphorylation on S1014 due to Serine-to-Alanine mutation was generated on the FVB strain background. These mice showed stereotypical, circling behavior, a plausible sign of autistic behavior. The project aims to study the role of MET phosphorylation site S1014 in the impairment of synapse formation and neuronal outgrowth causing a cognitive decline in ASD.

Methods. A battery of behavioral tests was built to study cognitive alterations in mice deficient in S1014 (HET and HOM) compared to WT animals. The battery aims to screen the differences in anxiety and locomotor activity (Open field), social domain (Reciprocal social interaction and Social dominance assays), repetitive behavior (Y-maze), and cognitive function (Fear conditioning). Nissl staining and neuronal density quantification were performed in the cortex, hippocampus, amygdala, and striatum.

Results. Our data indicate no differences in locomotor activity and repetitive behavior between the genotypes. However, HOM mice demonstrated a reduced level of anxiety and altered patterns of social dominance. Variation in average number of neurons of HOM and HET vs WT mice can be observed in different regions and layers of the hippocampus, which is consistent with the social paradigm described. Fear conditioning appears to be a not suitable test for FVB strain due to decreased learning ability.

Conclusion. The preliminary data suggest differences in the social domain between S1014-proficient and -deficient mice. Immunostaining will be performed to target specific neurons and brain regions after initial screening with Nissl staining. Further collection of behavioral data and test adjustments are ongoing.

Keywords: Autism Spectrum Disorders, MET, Behavior, Nissl staining

Functionnal characterisation of brain plasticity during optogenetic restoration in the retina

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Several retinal degeneration diseases (RD) result in progressive death of the photoreceptor cells such as age-related macular degeneration or retinitis pigmentosa affecting 1:4000 people. One of the main approaches to restore vision consists in using Optogenetics to grant photosensitivity to the surviving inner retinal cells, downstream of the degenerative photoreceptors.

Many optogenetic tools have been engineered accordingly, targeted at retinal bipolar or ganglion cells. They mainly involve microbial opsins, which are able to restore fast light processing vision but with poor sensitivity to low light intensity such as indoor light, and animal opsins (OptoGPCRs) with very good light sensitivity but very slow kinetics. Further, deep tissue optognetics is only achievable with highly invasive optic fibre illumination, since most optogenetic tools are activated by blue light that is massively scattered within tissue. Therefore, the optogenetic toolbox is missing temporally fully controllable, red-light sensitive OptoGPCRs.

A second key factor of vision restoration is the integration of the restored inputs into the existing network. Although many studies have investigated the retinal remodelling occurring during and after restoration, little attention has been given to functional changes in brain visual networks. It appears thus crucial to investigate what functional changes occur during vision restoration to predict the translational outcomes of optogenetic therapies in RD patients

The present project aims to design and implement new generation of light sensitive GPCRs and study vision restoration during optogenetic therapy in mice model of retinal degeneration at the cognitive level.

Keywords: Optogenetics Vision Restoration plasticity functionnality GPCRs

Top-down and bottom-up interactions at the posterior parietal cortex

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The world around us is full of different sensory stimuli. Processing and perception of these stimuli enables us to subsequently take necessary actions to respond or interact with them. Sensory perception can be represented as the comparison between feedforward bottom-up sensory information and feedback top-down expectations of these sensory stimuli. A balance between these two processes enables us to build a reliable representation of the external world. Higher-order cortical areas are involved in generating this representation and we are particularly interested in the posterior parietal cortex (PPC), an associative structure situated between the somatosensory (S1), auditory (A1) and visual cortex. It was recently shown that a subset of PPC neurons can respond to mismatches in audio tactile sensory sequences. We hypothesize that these mismatch neurons report the balance between the bottom-up (sensory input from S1 and A1) and top-down inputs (feedback from premotor M2). To test our hypothesis, we combine two-photon microscopy with novel analytical tools to measure cortical dynamics during sensory perception in mice. We developed a functional intrinsic imaging system to localize PPC. We have modified and adapted CaImAn, a calcium imaging analysis pipeline, to detect and track neuronal and axonal activity over multiple sessions and days. This enables us to effectively measure bottom-up and top-down inputs at the PPC during the formation of sensory associations.

Keywords: sensory perception, auditory, tactile

Basic Research Human Abstracts:

Physiological responsiveness to phase-locked auditory stimulation during SWS predicts increases in episodic memory performance in older adults

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Background

Previous research suggests that phase-locked acoustic stimulation (PLAS) during slow wave sleep (SWS) is able to boost ongoing oscillatory activity and – as a downstream effect – improve sleep-dependent memory consolidation. Due to the assumption that SWS disturbances could accelerate memory decline in aging as well as the accumulation of amyloid-beta peptides, older adults – especially those at risk of developing Alzheimer's Disease - might profit most from such interventions.

Methods

In this study, 28 healthy participants (age: 61-80 years, M = 69.3; 23 female) were randomly allocated to an intervention or control group. Participants completed one baseline night and three consecutive experimental nights with high-density EEG measurements. The intervention group received PLAS during experimental nights and sham stimulation during the baseline night. In the control group sham stimulation was applied in all four nights. In the evenings before and the mornings after experimental nights, as well as on a one-week and three-months follow-up session, participants completed a face-occupation association memory task.

Results

In the intervention group but not in the control group, PLAS induced a physiological response in form of an entrained a slow-wave peak in all three experimental nights compared to the baseline night. There was no overall difference in memory performance between the intervention and control group. However, a linear regression model showed that within the intervention group the physiological response to PLAS predicted memory performance: the higher the amplitude of the entrained slow wave peak, the better participants' memory performance. This relationship was statistically significant starting on the morning of the second experimental night ($p_{E2\_morning} = 0.012$) until the first follow-up ($p_{E3\_evening} = 0.021$, $p_{E3\_morning} = 0.034$, $p_{FU1} = 0.027$). Responsiveness to stimulation did not correlate with age, education, sleep quality, or other cognitive assessments.

Conclusions

PLAS is able to entrain slow oscillatory activity in older adults and the degree to which participants physiologically respond to the stimulation predicts increases in overnight memory performance. These results indicate that PLAS could be developed into a non-invasive and inexpensive tool to battle cognitive decline.

Keywords: Slow wave sleep, acoustic stimulation, cognitive decline

Improving sleep to prevent cognitive decline

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Background

During slow-wave sleep (SWS), the deepest sleep stage, memory is strengthened and metabolic waste-products like amyloid beta are cleared from the brain. With increasing age, sleep naturally becomes more fragmented and disrupted, leading to a loss of SWS. Disrupted sleep has been indicated as an early, modifiable risk factor for cognitive decline. Individuals with mild cognitive impairment and dementia suffer particularly from this fragmentation. In return, impairments of sleep, especially SWS, are likely causally linked to cognitive decline, creating a vicious cycle. We hypothesize an improvement of SWS would allow the brain to recuperate, potentially decelerating cognitive decline and breaking the vicious cycle.

Methods

We use auditory closed-loop stimulation to boost slow-wave activity during sleep.

Results
Preliminary data show that the strength of response as indicated by the amplitude of boosted slow-wave activity predicts increases in memory performance.
Conclusions
It is important to determine the factors that predict who might profit from this intervention and who might not. To this aim, we devised a two-pronged approach to validate and extend our research protocol. First, to validate our results, healthy participants that already underwent our intervention are re-tested. This will help identify intra-individual factors that might predict responsiveness to our intervention and gauge potential side effects. Next, we extend our protocol to include individuals with increased risk of developing dementia to test feasibility of our intervention with individuals who are most in need of it. Our goal is a non-invasive, low-cost, auditory tool to improve SWS and combat cognitive decline.

A systematic and qualitative evaluation of touch sensibility via robotic training

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More than half of stroke survivors experience sensory loss, which negatively impacts their independence and life quality. Additionally, the sensory loss is associated with a poor neurorehabilitation recovery prognosis. Despite the adverse effects of sensory loss, somatosensory training is not the standard of care and receives less attention than motor recovery. The lack of therapy time and limited access to appropriate somatosensory training guidelines might be behind the lack of sensory rehabilitation. This has been aggravated in the last year due to the COVID-19 pandemic.

To fill the gap in current sensorimotor rehabilitation, we developed a sensory discrimination task to characterize and train touch sensibility via the perception of virtual textures using a haptic robotic device with minimal therapist supervision. We run an experiment with 36 healthy participants to investigate: 1) the system reliability, and 2) the effectiveness of somatosensory training on participants' touch sensibility. On a three-day experiment, participants actively and passively (i.e., assisted by the robot) explored the virtual textures. We hypothesized that improvement in touch sensibility would not differ between active and passive exploration.

The first experimental session included two baselines per condition (i.e., active or passive exploration). The following training sessions included a baseline, training, and retention phases per condition. We evaluated the intraclass correlation coefficient (ICC) between the first two baselines for each condition to evaluate the system's reliability. Additionally, to assess the enhancement of touch sensibility after training, we compared changes between baseline and retention for the proportion of correct responses within each condition and compared these differences between conditions.

We found that our system has a poor to moderate reliability for active and passive conditions (active [ICC(2, k) = 0.5, 95% CI = [-0.2, 0.83], p=0.07], and passive [ICC(2, k) = 0.52, 95% CI = [-0.26, 0.82], p=0.05]). We found significant training effects for active [X^2(1,35) = 4.24, p = 0.04], and passive [F(1,35) = 15.56, p < 0.001]. Finally, we found no significant differences between conditions [F(1,35) = 1.00, p=0.32].

Robotic training may be a powerful tool for treating somatosensory loss with minimal supervision. However, the system's reliability has to be considered.

Keywords: psychometrics, sensory, rehabilitation, touch, robotics

Local slow wave activity in regular sleep reveals individual risk preferences

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In many everyday life situations, we have to make decisions under varying degrees of risk. Even though previous research has shown that the manipulation of sleep affects risky decision-making, it yet remains to be understood how regular, healthy sleep relates to risk preferences. Therefore, we investigated the relationship between individual, temporally stable neural sleep characteristics and individual differences in risk preferences in healthy adults. Sleep data were collected using a portable high-density EEG at participants' home. Results revealed a significant negative correlation between local sleep depth, as reflected in slow-wave activity (SWA) in a cluster of 5 electrodes located over the right prefrontal cortex and risk-taking behavior. This finding remained significant when controlling for total sleep time. Moreover, the association between SWA over the right prefrontal cortex and risk preferences was very similar in all sleep cycles. Our findings suggest that sleep depth in the right prefrontal cortex, an area involved in self-regulation, might serve as a dispositional indicator of lower self-regulatory abilities, which is expressed in greater risk-taking behavior.

Keywords: risk preferences, neural trait, individual differences, slow-wave activity, deep sleep

"Tricking the brain" using immersive VR: Modifying the self-perception over an embodied avatar influences motor cortical excitability and actions

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To offer engaging neurorehabilitation training to neurologic patients, motor tasks are often visualized in virtual reality (VR). Recently introduced head-mounted displays (HMDs) allow to realistically mimic the subject's body from a first-person perspective (i.e., avatar) in a highly immersive VR environment. In this immersive environment, subjects may embody avatars with different body characteristics. Importantly, body characteristics impact how people perform actions. Therefore, alternating body perceptions using immersive VR may be a powerful tool to promote motor processing in neurologic patients. However, the ability of the brain to adapt motor commands based on a perceived modified reality has not yet been fully explored. To fill this gap, we "tricked the brain" using immersive VR and investigated if multisensory feedback modulating the physical properties of an embodied avatar influences motor brain networks and performance.

Ten healthy participants were immersed in a virtual environment using an HMD, where they saw an avatar from first-person perspective. We slowly transformed the surface of the avatar (i.e., the "skin material") from human to stone. We enforced this visual change by repetitively touching the participant's real arm and the avatar's arm with a (virtual) hammer, while progressively replacing the sound of the hammer against skin with stone hitting sound using loudspeakers. We applied single-pulse TMS to evaluate changes in motor cortical excitability associated with the illusion. Further, to investigate if the "stone illusion" affected motor actions, participants performed a reaching task with the human and stone avatar. Questionnaires assessed the subjectively reported strength of embodiment and illusion.

Our results show that participants experienced the "stone illusion": They rated their arm as heavier, colder, stiffer, and more insensitive when immersed with the stone than human avatar, without the illusion affecting their experienced feeling of body ownership. Further, the illusion strength was associated with enhanced motor cortical excitability and higher reaching velocities, indicating that participants may have physically mirrored and compensated for the embodied body characteristics of the stone avatar. Together, immersive VR has the

potential to influence motor brain networks and actions by subtly modifying the perception of reality, opening new perspectives for the motor recovery of patients.

Keywords: Virtual reality, Stroke, Embodiment, Body Perception, Motor Cortex

Providing task instructions during motor training enhances performance and modulates attentional brain networks

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Learning a new motor task is a complex cognitive and motor process. Especially early during motor learning, cognitive functions such as attentional engagement are essential, e.g., to discover relevant visual stimuli. Drawing participant's attention towards task-relevant stimuli – e.g., with task instructions using visual cues or explicit verbal information – is a common practice to support cognitive engagement during training and, hence, accelerate motor learning. However, there is little scientific evidence about how visual or verbal task instructions affect attentional brain networks during motor learning. In this experiment (https://clinicaltrials.gov/ct2/show/NCT04759976), we trained 36 healthy participants in a virtual motor task: surfing waves by steering a boat with a joystick. We measured the participants' motor performance and observed attentional brain networks using alpha-band electroencephalographic (EEG) activity before and after training. Participants received one of the following task instructions during training: 1) No explicit task instructions and letting participants surf freely (implicit training; IMP); 2) Task instructions provided through explicit visual cues (explicit-implicit training; E-IMP); or 3) verbally explicit commands (explicit training; E). We found that providing task instructions during training (E and E-IMP) resulted in less post-training motor variability – linked to enhanced performance – compared to training without instructions (IMP). After training, participants trained with visual cues (E-IMP) enhanced the alpha-band strength over parieto-occipital and frontal brain areas at wave onset. In contrast, participants who trained with explicit commands (E) showed decreased fronto-temporal alpha activity. Thus, providing task instructions verbally (E) or visually (E-IMP) leads to similar motor performance improvements by enhancing activation on different attentional networks. While training with visual cues (E-IMP) may be associated with visuo-attentional processes, verbal-analytical processes may be more prominent when verbal explicit commands are provided (E). Together, we suggest that training parameters such as task instructions modulate the attentional networks observed during motor practice and may support participant's cognitive engagement, compared to training without instructions.

Keywords: motor learning, cognitive neuroscience, neural biomarkers, attention, instructions

Investigating the functionality of miRNAs in Wharton's jelly-derived small extracellular vesicles (sEV) and their potential role in neuro-regeneration

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Preterm birth is the leading cause of childhood morbidity and mortality with underlying neurological complications such as perinatal white matter injury (WMI). WMI results in long-term neurodevelopmental and neurobehavioral disabilities. It arises mainly after hypoxia-ischemia and inflammatory insults to the developing brain during a vulnerable period of the brain's myelinating cells. Failed myelination during white matter

development occurs. Until now, there is no cure for premature WMI. Recently, our research group and others have shown promising results towards using mesenchymal stromal cell derived small extracellular vesicles (MSC-sEV) as a therapeutic approach for neuronal injuries. MSC-sEV carry small non-coding RNA such as microRNAs (miRNAs). MicroRNAs can interact with mRNAs and might interfere with signaling pathways involved in premature WMI. Thus, we hypothesize that miRNAs, released by sEV upon uptake in their target cells, have a key function in the observed beneficial effects of MSC-sEV.

To investigate our hypothesis, we isolated MSC from the connective tissue of human umbilical cords, the so-called Wharton's jelly. sEV were purified from these cells using ultracentrifugation, followed by size-exclusion chromatography (SEC). The fractions were characterized by the expression of sEV markers using western blot analysis and miRNAs by quantitative PCR.

The SEC fractions with the highest protein content showed positive signals for the sEV markers CD81 and CD63. No cellular contamination was observed (no signal for GM130 or Grp94). These fractions contained high amounts of miRNAs, such as miR-21-5p, miR-22-5p, miR-27b-3p or let-7f-5p compared to WJ-MSC.

The targets of the highly abundant miRNAs in the sEV fractions play a role in apoptotic or inflammatory pathways and drive oligodendrocyte differentiation. Therefore, these miRNAs might influence WMI outcomes.

As a further perspective, functional analysis of the miRNAs antagomir *in vitro* assays and dual luciferase assays will be performed.

Keywords: white matter injury, small extracellular vesicles, microRNA

Probing cortical excitability in humans with epilepsy

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Background: Epilepsy is a neurological disorder characterized by recurrent seizures, which stem from abnormal neuronal activity in the cortex. 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 is done by recording intracranial EEG. We hypothesize that additionally probing of the cortex, through the injection of small electrical currents over the same electrodes, enables more precise localization of the epileptic focus.

Methods: In this study, we used two stimulation protocols to analyze the effect of different parameters on cortico-cortical evoked potentials (CCEP) in patients undergoing the icEEG presurgical evaluation. The protocols are repeated over night and at the end of the patient's hospital stay when benzodiazepine is given as part of the clinical routine.

(P1) Single pulse electrical stimulations (SPES) with intensities ranging from 0.2 – 12 mA are sent to calculate a gain curve.

(P2) Paired pulse electrical stimulations (PPES), which add a conditioning pulse (1, 2, 4 mA) before the probing pulse (2mA), are sent to demonstrate the dependency on ongoing cortical dynamics. Time between the two pulses is ranging from 15 to 1600 ms (IPI, Inter-pulse-interval)

Results: SPES demonstrate non-linear relationship between stimulation current and CCEP amplitude resulting in a sigmoid curve with floor and ceiling effects. PPES in three patients show nonlinear dynamics, with dependence on the current conditions of the brain network, by inducing intracortical suppression or facilitation (lower/higher CCEP magnitude than SPES reference) depending on condition pulse intensity and IPI. These preliminary effects are enhanced/weakened in certain connections by the different brain states (sleep, medications) and at certain times of the day, which may suggest the effect of the circadian rhythm on cortical excitability.

Conclusion: SPES and PPES are simple means of probing different aspects of cortical excitability. They can easily be delivered around the clock to monitor cortical excitability over time. 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.

Cerebral vascular compliance explained by variation of arterial intramural outflow sliding chamber length as driven by the nasal ganglion invaded by SARS-CoV-2 in dysorthostasis.

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Cerebral Intramural Reverse Arterial Flow (CIMURAF) shows up in rodents (Cserr 1974-1984) as the quickest path of cerebral clearance of e. g. Abeta from the brain's interstitial fluid (Szentistvanyi I, et al. 1984; Carare et al., 2008). An unsound pulsatile model was replaced by a muscular model based on a postulated hidden "aortic blueprint" of all arteries (since molluscs) by realizing the capacity of arterial intramural interlamellar alternate sense contractions to wring the wall through hyperboloid embayments confining sliding segments acting as rapid centrifugal fluid carriers (Treviranus 2016 – 2020). Later muscular models have eschewed detailed muscular specifications. The scant perivascular neuroscience as to the acting neuro-generators points to the pterygopalatine ganglion's (PPG) twice 70.000 cells and 4000 efferents to the major cerebral arteries and to muscarinic and chessboard-like nitrergic innervations, possibly providing coronal segmental contractions. While CIMURAF provides the only present model of the established intramural transport (to the neck's arterio-intramural lymphatics) its effects on a parallel adventitial flow (through radial shutters), on the (at times failing) clearance of signals and cells otherwise disrupting the blood-brain-barrier, and on arterial compliance merit further research also into the associated Idiopathic Intracranial Hypertension. The PPG might also provoke shame-like behavioral arrests through the suspension of a muscarinic inhibition of abluminal mast cells via the inhibitory Suzuki-link communicating submissive preparatory biting-inhibition via V3-to-V1-trigeminal cross-talk.

PA-Sequelae of Covid-19 direct attention on trajectories resembling chronic fatigue syndromes (ME/CFS) pivoting on debilitating Orthostatic Intolerance (OI). Normal orthostasis induces autoregulation through rapid "compliance" through a till date mysterious immediate arterial change in distensibility – only followed by a change in diameter (resistance) moderately preserved in OI (Brassard 2021). As a spin-off of a recent review of LongCovid-19 (Treviranus 2021) arterial "compliance" here is proposed to be generally provided by a quick and sliding variation in the length the PPG imposes on the draining CIMURAF-segments. Such lengthening and shortening of chambers will result in immediate softening and stiffening of the "compliance" with the orthostatic or pulsatile load. Covid-19 supports this mechanism through its early assault on the PPG (in deer mice) in proportion to dysosmia, but not neuropathology.

Keywords: PASC/long-Covid19, Orthostatic Intolerance, pterygopalatine ganglion, Cerebral IntraMUral Reverse Arterial Flow, cerebral interstitial drainage

Should I see the robot? Using HMD to hide or show the rehabilitation robot

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Rehabilitation robots that assist patients' movements during therapy are often combined with virtual reality (VR) to increase patients' motivation. Recent studies proposed that head-mounted displays (HMDs) are a promising visualization technology for rehabilitation interventions, as they allow a naturalistic movement visualization, possibly increasing other user affects crucial to enhance therapy, e.g., presence, embodiment, and attention. However, rehabilitation robots are generally invisible in the virtual environments (VEs). This missing visual information combined with the haptic sensation generated by the robot might create a visuo-haptic sensory mismatch, whose impact on users is still unknown. To evaluate the visuo-haptic conflict's impact on user affects, we developed a path-tracing task using an HMD and a commercial rehabilitation robot, which was either visually reproduced in the VE or not and which either assisted the movements or not. Twenty-eight healthy participants practiced the path-tracing task with either a visible and invisible robot, and with and without assistance, while their performance and visual attention (using an eye-tracker) were measured. After each task, they answered questionnaires to measure their motivation, presence, and embodiment. When the robot was invisible, we hypothesized that: (1) participants would report higher motivation, through a higher

perceived competence, especially when they are not assisted and (2) that the presence and embodiment would be reduced, especially when participants are assisted, due to the visuo-haptic conflict.

Contrary to our expectations, the robot's visibility did not affect the motivation, presence, embodiment, nor task performance, independently of the assistance. However, higher effort/importance was found with a visible robot, independently of the assistance. Further, when the robot was visible, participants looked more at the path, but the time spent looking at the space where the physical robot is (visible or not) did not change. Interestingly, most of the participants did not report to have noticed the change in robot's visibility. The assistance seemed to increase the motivation and decrease the presence and embodiment, even with the visible robot. In conclusion, our results indicate that the VE does not need to visually reproduce the rehabilitation robotic device, simplifying the design of VEs that can be employed with different robotic devices.

Keywords: Immersive VR, Head-mounted displays, rehabilitation robot, motivation, presence, embodiment, visual attention

Using cryo-ET to observe liquid-phase Rab3 function and location

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Connectors are pleomorphic structures that interlink majority of SVs in reserve pool, have a wide distribution of lengths (almost 5–30 nm). However, uncovering the composition and function of connectors is far from complete. We thought of using ferritin as the label protein because it can bind iron intracellularly, which is well visible in cryo-Electron Tomography. For labelling we use the FKBP and FRB system. FKBP can label our targeted protein and FRB can label the Ferritin. When we put the rapamycin, they can bind together. Some proteins may be part of connectors such as Synapsin, F-actin, Rab3A, SH3 domain containing proteins. In order to address our first hypothesis, we firstly label RAB3A with ferritin.Rab3A liquid phase may be functionally relevant in the synaptic vesicle turnover and neurotransmitter exocytosis regulation.Until now there are no paper report about the structure of liquid-liquid phase like droplet. We will use the cryo-Electron tomography to uncover this phenomenon.

Association between sleep macro- and micro-architecture and the measures of verbal and figural divergent and convergent thinking

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Sleep has been linked to multiple important functions including learning and memory consolidation. To date, only few studies investigated the association between sleep and creative behavior. While there is an indication that different aspects of creativity correlate with distinct sleep stages, to our knowledge no study to date investigated the association between the performance in verbal and figural divergent (DT) and convergent thinking (CT) and sleep macro- as well as micro-architecture.

Forty healthy adults (age range 18-40, 21 females) participated in two sessions separated by one week. Whereas the first session included verbal and non-verbal intelligence and sleep disorder screening, the second session assessed verbal and figural DT and CT, as well as resting-state and over-night 256-channel EEG. Participants' sleep behavior was tracked between the sessions by means of an actigraphy device and a daily filled out sleep questionnaire.

On a macro-level, an increase in N1 sleep was associated with increased fluency in verbal DT ($r_s(40)=.331$, $p=.037$). While an increase in N2 sleep was positively correlated to verbal creative problem solving in CT ($r_s(40)=.341$, $p=.031$), an increase in N3 sleep was associated with higher scores in figural DT ($r_s(40)=.320$, $p=.044$). Moreover, an increase in REM sleep was associated with a better performance in figural CT ($r_s(40)=-.352$, $p=.026$). On a micro-level, higher originality in figural DT was correlated with lower slow wave power ($r_s(40)=-.434$, $p=.005$). While the current findings confirm the link between creativity and sleep, they emphasize that different aspects of creativity are distinctly associated with sleep macro- and micro-architecture.

Keywords: macro- and micro-architecture of sleep, verbal and figural divergent and convergent thinking, hd-EEG

Improved objectivity by applying word vectors for creativity assessment

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Divergent thinking (DT), as a compound of creativity, refers to an ability to produce multiple solutions to a given problem. A possible means to measure DT is the Associative Fluency Task (AFT) where participants are instructed to produce associations to a prompt word. The output of such DT tasks is typically assessed by the number of produced ideas (i.e., fluency), their originality as well as their semantic proximity (i.e., flexibility). Whereas there are objective means to assess fluency and originality, flexibility is often subjectively rated, hence influenced by inter-individual variations in the perception of semantic distances.

In this study, semantic distances between words were first quantified by applying word vectors of the German language that were trained using a predefined set of parameters. In the next step, these word vectors were adapted for the purpose of creativity assessment by composing a more diverse text corpus for the training and by accounting for homonyms and synonyms to circumvent context ambiguities.

The generated word vectors were applied on the AFT data of 50 healthy subjects. Compared to the pre-trained vectors, the adapted vectors indicated higher correlations not only to the human ratings, but also to the ratings extracted from GermaNet, a semantic network for the German language. Given these preliminary results, the developed measure has a great potential to assess the output of DT tasks more objectively.

Clinical Research Abstracts:

The impact of age at pediatric stroke on long-term cognitive outcome

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Background and Aim: Pediatric arterial ischemic stroke is a rare event but is accompanied by an increased risk for cognitive sequelae. The association between age at stroke and long-term cognitive outcome remains however unclear. Here, we investigated the impact of age at pediatric arterial ischemic stroke on long-term cognitive outcome in order to identify patients particularly at risk for the development of long-term cognitive sequelae.

Methods: This cross-sectional study included patients in the chronic phase of stroke (> 2 years after stroke) previously diagnosed with neonatal or childhood arterial ischemic stroke and a control group. Participants with active epilepsy, severe handicaps, or behavioral problems hindering the cognitive assessment were excluded. Several cognitive domains, including intelligence, executive functions (working memory, inhibition, and cognitive flexibility), processing speed, memory, letter fluency, and visual-motor skills were assessed with neuropsychological tests. Cognitive long-term outcome was compared across patients after neonatal stroke (stroke between 0 and 28 days of life), early childhood stroke (stroke between 29 days and < 6 years), and late childhood stroke (stroke between ≥ 6 and < 16 years).

Results: 52 patients after neonatal or childhood arterial ischemic stroke (median age: 15.3 years, IQR = 10.6 – 18.7) and 49 healthy controls (median age: 13.6 years, IQR = 9.8 – 17.2) met the inclusion criteria. Cognitive outcome was significantly worse in the pediatric stroke group compared to the control group. A non-linear effect of age at stroke (irrespective of lesion size and lesion location) was found for cognitive flexibility, processing speed, and verbal learning with early childhood stroke (29 days to < 6 years) showing significantly worse cognitive outcome compared to neonatal or late childhood stroke ($p < .05$, FDR-corrected).

Conclusion: Age at stroke is an important factor for post-stroke recovery and modulates long-term cognitive outcome irrespective of lesion size and lesion location. Children after early childhood stroke are at particular risk for alterations of long-term cognitive functions.

Keywords: Pediatric stroke, cognition, rehabilitation

Usability of new interactive hand training devices in Parkinson's disease: A pilot study

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Background: Patients with Parkinson's disease (PD) often suffer from impairments in hand function, which only slightly improve after dopaminergic treatment. Traditional rehabilitation protocols may further improve hand function, however on the long term they often suffer from low adherence rating. Newer interactive game-based devices may overcome this issue by offering an attractive, motivating hand training modality. This pilot cross-sectional study aimed to evaluate the usability of two new interactive game-based hand devices (Gripable and Smart Egg) in both healthy adults as well as in PD patients.

Methods: Thirty-nine healthy adults (aged 48.4 ± 14.9, MoCA = 26.08 ± 3.12) and 8 patients with Parkinson's disease (63.2 ± 10.3, MoCA = 26.13 ± 4.29, H&Y I-III) participated in this study. Besides standardized usability

measures (System Usability Scale, SUS), the state of flow (measured by Flow State Scale for Occupational Tasks, FSSOT) after one training session and the effect of cognitive abilities (measured by Montreal Cognitive Assessment, MoCA) on device usability were evaluated.

Results: High SUS scores were obtained both in healthy subjects (80.32 ± 13.73, Gripable) as well as PD patients (74.35 ± 10.84, Gripable; 79.5 ± 6.95, Smart Egg). Similarly, high FSSOT scores were achieved after one training session (> 44, maximum score 55). FSSOT scores correlated significantly with SUS scores ($r = 0.44$, $p = 0.003$). Finally, MoCA did not correlate significantly with SUS scores ($r = 0.41$, $p = 0.05$).

Conclusion: The present study shows high usability for both interactive hand training devices, and this for both healthy subjects and PD patients. The high flow experience after one training session indicates that subjects were very involved and perceived the gameplay setting as highly motivating, even for the subjects with more pronounced cognitive deficits. Interactive game-based hand training (using Gripable or Smart Egg) yields promising results and its impact on hand function in patients with PD will need to be thoroughly evaluated in future studies.

The Neurotec Loft: An Instrumented Apartment to Monitor Motor and Non-Motor functions

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Introduction: The increasing life-expectancy leads to a higher number of people at risk for age associated and neurodegenerative disorders (e.g., Parkinson, Alzheimer's disease) and thereby the need of institutional care. Further, the behaviour and activities of daily living at home (i.e., motor, and non-motor functions) are an indicator for the change in health status. Thus, the home-monitoring over a prolonged time of motor- and non-motor functions in an home like environment by contactless and unobtrusive sensors are promising technologies to foster independent living and maintaining quality of life.

Method: The instrumented apartment called NeuroTec Loft is a modern 3.5 room apartment located at the Sitem-Inselspital in Bern. The instrumented apartment is equipped with contact less sensors in order not to disturb patients and healthy subjects and thus to simulate natural behaviour like living at home. In the instrumented apartment over 200 sensors such as radar sensors, lidar sensors, infrared cameras, pressure sensors, flow meters, video cameras are installed. In the past year the assessment of motor, and non-motor functions system was validated in 6 healthy subjects.

Results and Discussion: The results showed that the sensor system was measuring accurately over a prolonged time, allowed to have a standardized environment to compare between subjects and to monitor motor, and non-motor functions in everyday life. First patients' studies will start in the beginning of 2022 (e.g., the investigation how deep brain stimulation influences non motor symptoms, the investigation of performance of activities of daily living in patients after stroke or traumatic brain injury).

Conclusion: Overall, the instrumented apartment allows to advance science in terms of the understanding of the phenotype of neurodegenerative diseases, to detect diseases at an early stage or to indicate a sudden deterioration in health in an home like environment. Thus, the instrumented apartment has a great potential to increase quality of life of our aging society and patients with neurodegenerative diseases.

Keywords: Instrumented Apartment, Sensors, Motor and non-motor functions, Activities of daily living

Immunotherapies and COVID-19 mortality: a multidisciplinary open data study

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Background: Evidence on mortality risks associated with immunotherapies for the treatment of autoimmune diseases during the SARS-CoV2 pandemic are still limited. We here analyzed fatality reports to the FDA Adverse Event Reporting System (FAERS), an open access pharmacovigilance database, on immunotherapies and COVID-19. We additionally analyzed socioeconomic and epidemiological data from Oxford University's "Our World in Data" and the World Bank.

Methods: 2103 international cases were retrieved from FAERS and a multivariable logistic regression was performed. We adjusted for sex, age, region, month of report to FDA and medication. Hospital beds/1000 persons/per country and health expenditure per person/per country served as socioeconomic, monthly COVID-19 case fatality rate/per country, new COVID-19 cases and deaths/per population/per month served as controls.

Result: The most frequent indications for immunotherapies were inflammatory joint disease (40.2%) and Multiple Sclerosis (22.5%). Anti-TNFα (34%) followed by anti-CD20 therapies (18.4%) were used most often. Besides higher age and male sex, anti-CD20 therapies were significantly associated with a higher risk of death (OR 4.5; 95%-CI 2.6 – 7.9; p<0.001), whereas anti-IL 17 therapies had a reduced mortality risk (OR 0.2; 95%-CI 0.04 – 0.67; p=0.01) using anti-TNFα as a reference.

Conclusion: Using FAERS and a multidisciplinary approach for risk prediction, we identified an increased mortality risk associated with B cell depleting therapies, which is in line with other cohort studies, and a mortality risk reduction with anti-IL 17 therapies, previously unreported. Adjusting for socioeconomic and regional epidemiologic variables affects prediction models of SARS-CoV2 outcomes and should be integrated in corresponding analyses.

Can robotic devices improve neurorehabilitation during a pandemic? Development of a novel device for minimally supervised sensorimotor upper-limb training

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Every year, millions of stroke survivors lose their functional autonomy due to upper-limb paralysis. After stroke, patients should engage in task-specific and high-intensity training to maximize recovery. Additionally, neuroscience suggests that realistic visual and somatic sensory information should both be considered in rehabilitation training. Robotic devices could potentially provide this kind of training, yet current robot-aided interventions mostly rely on abstract visual feedback, while somatic (tactile and proprioceptive) feedback is underutilized. There is increased interest in robotic devices for neurorehabilitation, yet, in the context of the current pandemic, we expect that the demand will continue to grow. If operated in a minimally supervised or unsupervised manner, robots could allow minimizing the contact between therapists and patients in a clinical setting or in telerehabilitation. This, however, is only achievable if robotic devices meet stricter requirements in terms of safety, usability, and ease of setup compared to today's standards.

To address current limitations in rehabilitation robotics, we are developing a novel clinical-driven robotic device for upper-limb rehabilitation that incorporates somatic feedback and can be employed in a minimally supervised setting. After surveying clinical personnel, we developed a prototype of a palmar device that is capable of fine haptic rendering (physically represent interaction forces with tangible virtual objects), and that introduces the following novelties: 1) Effortless installation of the patient's hand while offering finger motion from 180° flexion to full extension. 2) All fingers are supported through the full range of motion. 3) It guarantees physiologically correct finger movements for a large variety of hand sizes solely by using rapidly

exchangeable handles. While the design is currently being refined in collaboration with the Department of Neurology, Inselspital, Bern, we are developing virtual training tasks with rich rendered dynamics that will provide realistic sensorimotor information during motor training. The device will hence allow for simultaneous sensory and motor training and improve relevant upper-limb functions.

Our novel device paves the way for a new generation of hand rehabilitation devices that provide congruent visio-haptic sensorimotor information during training, while potentially allowing for minimally supervised or unsupervised rehabilitation training.

Keywords: neurorehabilitation, stroke, upper-limb rehabilitation, robotics, telerehabilitation

Cerebral blood flow and its association with cognitive and motor performance in pediatric cancer survivors - a study protocol

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Due to early diagnosis and improved treatment approaches, survival rates for pediatric cancer have increased up to 90%. Therefore, the focus of current research has turned to the adverse long-term effects of pediatric cancer and its treatment. Among other long-term sequelae, pediatric cancer survivors frequently experience cognitive and motor difficulties, likely due to the negative impact of cancer and its treatment on brain development. Previous research has shown that pediatric cancer survivors present functional and structural brain alterations. Up to date, little is known about the possible relationships between cerebral blood flow, cognition and motor abilities in pediatric cancer survivors. Hence, the aim of the present study is to investigate cerebral blood flow, cognitive functions, and motor abilities of pediatric cancer survivors and examine the associations between these three domains.

We included 41 children after non-central nervous system cancer (≥one year since end of cancer treatment) and a healthy control group (n = 44). All participants underwent MRI, including Arterial Spin Labeling, neuropsychological, and motor assessments. Global cerebral blood flow and region of interest analyses will be conducted using cortical regions of cerebral vascular territories and the relationships between cerebral blood flow, cognitive and motor performance will be analyzed.

The findings of this study will expand the understanding of the impact of pediatric cancer and its treatment on cerebral blood flow in relation to cognitive and motor performance. The results may thereby provide insight into possible underlying markers of long-term sequelae in pediatric cancer survivors.

Keywords: Pediatric cancer survivors, Arterial spin labeling, Cerebral vascular territories, Cognitive and motor performance

Leptomeningeal enhancement under different immunotherapies – a monocentric retrospective cohort study of 215 patients

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Introduction: Leptomeningeal enhancement (LME) in multiple sclerosis (MS) patients consists mainly of meningeal B cell follicle-like structures that are linked to cortical and subpial lesions.

Objective: To evaluate the evolution of LME as a new imaging biomarker of disease activity under treatment with different immunotherapies.

Methods: Retrospective analysis of clinical and MRI data (either 1.5 or 3 T) since 2018 regarding LME of 215 MS patients treated with ocrelizumab, rituximab or fingolimod in a tertiary neurological center.

Results: We evaluated 215 MS patients (mean age 43.3 years, range 18 – 79 years, 132/215 61% female, 21 (9.7 %) with primary progressive (PP) and 194 (90.3 %) with relapsing remitting (RR) MS). 126/215 MS patients (58.6 %) received anti-CD20 therapies, (21/126 rituximab and 105/126 ocrelizumab) and 89/215 (41.4 %) patients received fingolimod. Each patient had one MRI exam before initiation and at least one (range 1 - 7) during treatment (mean 4 MRI exams per patient). Mean disease duration was 99.1 months (range 5 - 456 months), mean EDSS was 2.5 (range 0 – 7). Mean number of prior immunotherapies was 1.1 (range 0 – 5). Mean observed treatment duration was 16 months for anti-CD20 therapies (range 1 - 56 months) and 50.3 months for fingolimod (range 5 – 115 months). Of the 126 patients with anti-CD20 therapies, 106 (84 %, 87 RR, 19 PP) patients had no LME, 11 (8.7 %, 9 RR, 2 PP) patients had persistent LME, whereas 9 (7.1 %, 8 RR, 1 PP) patients showed resolution of LME (all under ocrelizumab). Of the 89 RRMS patients treated with fingolimod, 84 (94.4 %) patients had no LME, 5 (5.6 %) patients had persistent LME, whereas none showed resolution of LME. Resolution of LME was significantly more frequent during ocrelizumab treatment compared to fingolimod and rituximab treatment ($p<0.05$).

Conclusion: We observed LME resolution under treatment with ocrelizumab, but not under treatment with fingolimod or rituximab. As LME plays an important role in cerebral gray matter pathology, further investigations and extensions to higher field strengths (UHF MRI), correlation with clinical phenotypes and comparison with other immunotherapies are needed.

Keywords: Multiple sclerosis, immunotherapies, leptomeningeal enhancement

Volume reductions in the limbic network in patients with paranoia

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Background

Paranoia is a frequent symptom in schizophrenia, which leads to tremendous individual burden and requires individualized treatment. Thus, early detection of paranoia is crucial to enhance the quality of life of patients. Here, we used a behavioral measure to detect paranoia and compared whole brain grey matter volume in patients with schizophrenia and healthy controls.

Methods

To test the effect of interpersonal distance (IPD) on grey matter volume we applied an interpersonal distance test on a total sample of 114 subjects (33 healthy controls, 81 schizophrenia patients). Next, we stratified our patient sample into subgroups of patients with normal and high IPD. We performed whole brain voxel-based morphometry between healthy controls, patients with normal IPD and patients with high IPD. We tested group effects using a one-way ANOVA and added age as a covariate and total intracranial volume as a global value. We calculated post-hoc tests using t-contrasts. Results were corrected for multiple comparisons ($p_{(FWE)} < .05$).

Results

The ANOVA revealed significant differences between groups in grey matter volume within the limbic system including bilateral hippocampus, amygdala, ventral tegmentum, and thalamic nuclei. Post-hoc comparisons, revealed significantly reduced volumes in hippocampus, thalamus, putamen, temporal gyrus, and cerebellum in patients with high IPD compared to patients with normal IPD and healthy controls. In contrast, no differences in grey matter volume were observed between healthy controls and patients with normal IPD.

Conclusion

Reduced grey matter volume in key limbic areas was associated with high IPD in patients with schizophrenia. Particularly the association with the hippocampus supports animal models of delusion formation. The results further demonstrate that grouping patients according to a marker of territorial behavior allows for testing structural abnormalities in the limbic network related to paranoia in psychoses. Behavioral markers may perform superior to clinical rating scales in identifying pathobiology within specific psychosis dimensions.

Keywords: Interpersonal Distance, Schizophrenia, Territorial Behavior, Psychosis, Grey matter

Slowed patients with schizophrenia lack deactivation of parietal regions during finger tapping

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Motor symptoms are frequent in patients with schizophrenia and present in different flavours, one of which is motor slowing. A sound understanding of its neural background may help improving future therapies for motor slowing in schizophrenia. Here, we performed task-fMRI using a finger-tapping task in slowed patients.

We included 24 slowed patients with schizophrenia (Salpêtrière Retardation Rating Scale-Score (SRRS) >15) and 34 healthy controls. All participants performed a task during fMRI, with four conditions: paced and fast thumb-index finger tapping and thumb alternating finger opposition. Performance was videotaped and taps were counted. We performed one-sample t-tests for each group to examine the underlying motor network and a two-sample t-test to examine between-group differences in activations.

Slowed patients with schizophrenia showed significantly lower tapping speed than controls in both unpaced conditions (Δ = -.80 (CI = -1.46; -.14) taps/s, p = .019; Δ = -.80 (CI = -1.32; -.28) taps/s, p = .003). Both groups showed activations in in left primary motor and sensory area, right cerebellum and SMA in all conditions. Both groups additionally recruited right primary motor and sensory areas in thumb-alternating finger opposition. Two-sample t-test revealed significant differences in bilateral superior parietal lobules. Post-hoc evaluation of raw BOLD-signals revealed that patients lack the deactivation of these regions that is observable in healthy controls.

Slowed patients with schizophrenia as defined by the SRRS also showed decreased finger-tapping speed. Activations in both groups were located in sensorimotor areas. Patients do not show a deactivation in parietal regions opposed to controls. This may indicate compensatory recruitment of additional neural resources or disruption of networks.

Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma

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An open challenge in consciousness research is understanding how neural functions are altered by pathological loss of consciousness. To maintain consciousness, the brain needs synchronized communication of information across brain regions, and sufficient complexity in neural activity. Coordination of brain activity, typically indexed through measures of neural synchrony, has been shown to decrease when consciousness is lost and to reflect the clinical state of patients with disorders of consciousness. Moreover, when consciousness is lost, neural activity loses complexity, while the levels of neural noise, indexed by the slope of the electroencephalography (EEG) spectral exponent decreases. Although these properties have been well investigated in resting state activity, it remains unknown whether the sensory processing network, which has been shown to be preserved in coma, suffers from a loss of synchronization or information content. Here, we focused on acute coma and hypothesized that neural synchrony in response to auditory stimuli would reflect coma severity, while complexity, or neural noise, would reflect the presence or loss of consciousness.

Results showed that neural synchrony of EEG signals was stronger for survivors than non-survivors and predictive of patients' outcome, but indistinguishable between survivors and healthy controls. Measures of neural complexity and neural 'noise' were not informative of patients' outcome and had high or low values for patients compared to controls. Our results suggest different roles for neural synchrony and complexity in acute coma. Synchrony represents a precondition for consciousness, while complexity needs an equilibrium between high or low values to support conscious cognition.

Keywords: Coma, Cardiac arrest, Outcome prognosis, Neural synchrony; Neural complexity

The role of negative symptoms and anxiety in loneliness in patients with schizophrenia

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Background

Loneliness or `perceived social isolation´ can have critical health consequences. People with psychosis are particularly vulnerable to loneliness, with reports demonstrating loneliness in up to 80% of patients during a one-year period. Patients with negative symptoms and anxiety may be particularly vulnerable, as they are more prone to social withdrawal. Here, we aim to test whether severity of negative symptoms and levels of anxiety contribute to feelings of loneliness in patients with schizophrenia.

Method

We recruited 70 patients with schizophrenia at the University Hospital of Psychiatry and Psychotherapy in Bern, Switzerland. Current feelings of loneliness, objective and subjective ratings of negative symptoms, as well as state- and trait-levels of anxiety were assessed with the UCLA loneliness scale, the brief negative symptom scale (BNSS), the self-evaluation of negative symptoms scale (SNS), and the State-Trait Anxiety Inventory (STAI). Two two-stage hierarchical multiple regressions were performed, to independently assess the predictive capacity of subjective negative symptoms (regression one, stage one) and objective negative symptoms (regression two, stage one) on current levels of loneliness in patients, with state- and trait-levels of anxiety as additional predictors (stage two in both models).

Results

The first regression indicated that self-reported negative symptoms accounted for 31% of the variance in current feelings of loneliness, while trait-anxiety accounted for 10% of loneliness above and beyond negative symptoms. The second regression indicated that objective ratings of negative symptoms did not significantly account for variance in current feelings of loneliness, while trait-anxiety accounted for 30% of loneliness, when controlling for objective negative symptoms.

Conclusion

Our results suggest that severity of negative symptoms and anxiety-levels significantly contribute to current feelings of loneliness in patients with schizophrenia. Interestingly, our results suggest that subjective rather than objective ratings of negative symptoms and trait- rather than state-anxiety most accurately predict current feelings of loneliness.

Keywords: Loneliness, Anxiety, Negative Symptoms, Schizophrenia

Importance of the cerebellum during gesture planning in schizophrenia – an fMRI study

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Background

Gestures are an essential part of communication, as they support verbal communication and transmit information on their own. Patients with schizophrenia often exhibit gesture deficits, greatly affecting their communication skills and social functioning. Gesturing relies on the coordinated interplay of motor- and speech-related brain regions, called 'praxis network', which has been reported to be altered in schizophrenia. Here, we examined the brain activation of schizophrenia patients and healthy controls when planning hand gestures during an fMRI task.

Methods

We included 41 stable outpatients with schizophrenia spectrum disorders and 28 age and gender-matched healthy controls. During fMRI, participants performed a gesture task that included 10 meaningless, 10 meaningful gestures and a control condition of 10 neutral sentences without any gestures. Participants had to plan and perform gestures in the scanner. Inter-stimulus intervals separated planning and execution phases. We analyzed brain activity during gesture planning contrasting meaningless gestures with no gestures (control sentences) for both groups using whole-brain voxel-wise one-sample t-tests. We also compared event-related activations between groups using whole-brain voxel-wise two-sample t-tests. We applied family-wise error correction for all tests.

Results

Within-group contrasts indicated that both patients and controls activated bilateral brain regions of the praxis network including the primary somatosensory, primary motor and premotor cortices, as well as the inferior and superior parietal lobules. In addition, between-group contrasts showed further activation in the right cerebellum and the left primary motor cortex in patients, but not in controls.

Conclusion

During the planning of meaningless gestures, patients demonstrated activation of the cerebellum, which is known to modulate language, cognition, and motor activity. This suggests that patients need to activate more neuronal resources than controls to successfully plan the given gesture. These findings suggest the importance of the cerebellum in nonverbal communication for individuals with schizophrenia. We expect further group differences to appear as more participants are included in the study.

Keywords: gesture, schizophrenia, psychosis, fmri, cerebellum

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.

Method: 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 13 neglect patients were measured with a mean age of 58.2 years.

Results: First of all the results revealed high usability with no side effects. Second, the results show for all patients a performance increase if auditory or combined cues were given. In the case of tactile cues, only patients without somatosensory impairment could profit from cueing. Furthermore, all cues seemed to help with the early orientation towards the target.

Conclusion: With these 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 show that multisensory cueing in virtual reality is possible in neglect patients, as different sensory modalities can be used. 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.

Keywords: Virtual reality, Stroke, Visual Neglect, Multisensory cuing, multimodal

Diminished slow wave activity in unmedicated adolescents with major depressive disorder

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Depression is very often accompanied by sleep complaints. Depressed individuals often suffer from disrupted sleep. In adolescents as well as adults with depression, studies have found changes in slow wave activity and sleep spindles. Due to samples with broad age ranges, different medication status and variable severity of depression, the findings have been inconclusive. The aim of the present study was to examine sleep neurophysiology in an un-medicated sample of adolescents with and without major depressive disorder (MDD) using high-density sleep electroencephalogram (EEG). Thirty-nine adolescents with and without depression between the age of 14 and 17 years (mean 15.15 years, SD = 1.1; 25 females; 18 with MDD) participated in the present study. Based on a clinical interview participants were screened for MDD. The three days before the high-density sleep EEG (59 EEG derivations) was recorded, participants had to follow three sleep adaptation night ensuring at least 9 hours of sleep per night. An ANOVA with factors age, sex and group was used to determine statistical differences between the groups and slow wave activity (SWA) was calculated as power in the 0.6-4.6 Hz range.In our study, we found a significantly diminished SWA in adolescents suffering from depression as compared to those without depression. Thirty-three derivations distributed over different brain regions showed statistically significant differences. Effect sizes were large, with eta squared values for significant electrodes ranging between 0.11 to 0.28. The observed reduction in SWA in adolescents with depression was topographically more widespread and effect sized were larger compared to former studies. This might be explained by the recruitment of an un-medicated sample, the narrow age range and the moderate to severe depression, which may help reduce variability and furthermore, increases statistical power. Our results add to the existing literature showing a reduction of SWA in depression and further our understanding of the role of sleep in adolescent depression.

Keywords: sleep, EEG, depression, adolescent

The longitudinal association between sleep and depressive symptoms in adolescents

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The relationship between disrupted sleep and depression is complex and bidirectional. On one hand, sleep disruption (e.g. difficulty falling or staying asleep or waking up too early) is very common in individuals with depression, and on the other, disrupted sleep is a risk factor for the onset of mental health issues including depression. The aim of the present study was to assess the temporal association between sleep and depressive symptoms in a sample of un-medicated adolescents with and without major depressive disorder (MDD) using a longitudinal design. Our sample consisted of 29 adolescents between the age of 14 and 17 years of age (mean 15.1 years, SD = 1.7; 17 females; 11 with MDD). For a 12-month period participants wore an actigraph continuously and filled out questionnaires once per month via a secure online platform. Sleep quality was assessed using the Pittsburg Sleep Quality Index (PSQI) and depressive symptoms were assessed using the sum score of the Center for Epidemiological Studies - Depression Scale (CES-D). A cross-lagged panel design was used to assess the longitudinal relationship between sleep and depressive symptoms. One model was run for each of the following sleep measures: sleep onset latency, SOL; wake after sleep onset, WASO; total sleep time, TST measured via actigraphy and subjective sleep measured via the PSQI. The relation between depression and subjective as well as objective sleep measures was bi-directional with depression levels in the past month being a predictor for objectively ($\beta = 0.53$, $p < .001$) and subjectively ($\beta = -0.02$, $p < .05$) measured TST in the following month. Depression in the past month also predicted subjective SOL ($\beta = 0.03$, $p < .001$) and subjective sleep quality ($\beta = 0.02$, $p < .001$) in the following month. Conversely, objectively $\beta = 0.27$, $p < .05$) and subjectively ($\beta = 0.48$ $p < .001$) measured SOL in the past month was a predictor for depression in the following month. In many cases, sleep disturbances are viewed as a symptom or a consequence of a mental illness. Using a longitudinal approach, our findings show a bi-directional relationship between depression and sleep in adolescents where sleep problems are a risk factor for mental health problems and exacerbate sleep difficulties.

The associations of sleep and personality functioning indicate dimensionality in mental health

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Most psychiatric disorders in adolescence are associated with alterations in both sleep behavior and neurophysiology. However, changes to sleep are not limited to psychiatric diagnosis but have also been reported to a less pronounced extent in healthy adolescents and in sub-clinical samples. This finding suggests that, rather than being an exclusive feature of mental health problems, the link between sleep changes and mental health can be understood as a matter of degree. Therefore, the current study takes a dimensional approach to investigate the relationship between personality and sleep. Twenty-six medication free participants (10 with Major Depressive Disorder and 16 healthy controls) aged 14 to 17 years (mean = 15.2 (±1.1); 14 girls) were included in the study. The PID-5 was used to assess dimensions of personality: detachment, psychoticism, antagonism, disinhibition, and negative affect. Based on all night high-density (58 channel) sleep EEG recordings, power in the delta (0.6 to 4.6 Hz) and sigma (11 to 16 Hz) bands was computed, corresponding to slow waves and sleep spindles respectively. Stepwise regression analysis was performed to examine the associations between PID-5 dimensions and delta and sigma power. The Benjamini-Hochberg procedure was used to correct for multiple comparisons. Diminished delta power was associated with greater negative affect only for 28 electrodes over frontal, temporal, central and parietal regions ($0.03 < p < 0.04$). No associations between sigma power and any of the dimensions was found. The current study showed associations between negative affect and delta power independent of the other dimensions of personality functioning. On a general level, our findings support a dimensional view of mental health and add to the previous research pointing to diminished delta power in

depressed adolescents compared to healthy controls. We find neurophysiological evidence that personality functioning in youth can accurately be conceptualized as part of a continuum.

Keywords: sleep, EEG, adolescent, depression, personality

The sleep-stress association in adolescence - a long-term bidirectional relationship?

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Across all stages of human development, stress and sleep are intimately connected. As shown in animal models, stress exerts a negative influence on sleep. Stress is associated with both reduced sleep quality/duration, and conversely, changes to sleep behavior can lead to increased feelings of stress. However, in humans, the temporal associations between sleep and stress is unknown. Therefore, the current longitudinal study investigated the link between sleep and stress. The current sample consisted of 32 participants, thirteen with Major Depressive Disorder and nineteen healthy controls (mean = 15.13 (±1.13); 19 girls). Stress was measured using the Perceived Stress Scale (PSS), while sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI). The questionnaires were administered monthly using a secure online data capture. The sum score of the PSS and subjective sleep quality/duration derived from the PSQI were outcome variables. On average 10.41 months of data was available across participants (range = 2 to 15 months). The association between stress and sleep over time was examined by performing cross-lagged panel analysis. Higher stress levels in the past month were predictive of shorter sleep duration in the following month ($p < .001$), and conversely, reduced subjective sleep duration predicted higher stress ($p < .01$). Higher stress scores predicting future lower subjective sleep quality ($p < .001$), while lower reported sleep quality did not significantly predict subsequent feelings of stress. The findings of this study indicate reciprocal associations between stress and sleep duration over time; this relationship exits beyond psychiatric diagnosis in both healthy adolescents and depressed teens. Our results add to previous evidence in animal models suggesting a bidirectional association between sleep and stress.

Keywords: sleep, stress, adolescent, mental health

Characterization/optimization of the corneal stiffening technique named pulsed crosslinking

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Keratoconus is an eye disease where instead of having a normally round cornea it turns into a cone-like shape due to thinning. Corneal crosslinking (CXL) is a safe & effective technique for preventing the advancement of keratoconus and consists of application of riboflavin, its activation by means of UVA-light and reactive oxygen species (ROS) causing new bonds to form in the cornea's extracellular matrix.

This study provided experimental data on O_2 consumption during pulsed CXL by determining the O_2 profile at various depths, irradiances and pulsing schemes, to develop a new pulsing model for optimizing the clinical treatment.

In de-epithelialized porcine eyes, a probe was placed in different corneal depths to measure the local oxygen concentration. The sets of experiments were carried out in three different conditions: continuous CXL, symmetrical pulsed CXL and asymmetrical pulsed CXL at 3-30 mW/cm^2. The initial validation of the symmetrical

model was performed by reproducing the experimental data with the 10":10" pulsing scheme. Once the UV irradiation was initiated oxygen levels quickly descended and after cessation of the UV irradiation, oxygen was recovering quickly. In 300 µm the model perfectly fitted the experimental data for all powers. All model predictions start from higher values because of its initial calibration on continuous irradiation experiments but for the 300 µm lower maximum O_2 levels were noted. Experimental data for asymmetric model have a higher spread when compared to the symmetrical experimental data but the asymmetrical model fits the asymmetrical experimental data better than the symmetrical model fits the experimental symmetrical data. The oxygen consumption for 200 µm is higher when compared to the same irradiance for 300 µm. In both 200 and 300 µm there is statistically significant difference in 30 mW/cm^2, between the two different pulsing models.

In conclusion, the consumption of O_2 due to the laser is directly related to cross-link formation with laser power and pulse duration being optimized to avoid complete depletion of O_2inside the cornea. A limitation of this study concerns its ex-vivo nature as O_2 on the posterior cornea is also regulated by blood flow.

Keywords: keratoconus, CXL, pulsing, cornea, oxygen

Ocrelizumab-related Neutropenia: Effects of age, sex and bodyweight using the FDA Adverse Event Reporting System (FAERS)

Hammer, Helly

Introduction: Safety and efficacy of Ocrelizumab (OCR) have been evaluated in randomized controlled studies with infusion-associated reactions being the most prevalent adverse event. Whereas slight decreases in neutrophil counts occurred in 13-15% of patients during the pivotal trials, grade 4 neutropenia was observed in up to 1% of patients and can develop as late-onset neutropenia as already reported for Rituximab. Potential risk factors for OCR-related neutropenia are still unclear.
Aims: To investigate Neutropenia in OCR treated MS patients.
Methods: Safety data was retrieved from the open source data registry provided by the FDA Adverse Event Reporting System (FAERS; date of download 12th April 2021). Only data with OCR as the single suspected product used were included. Multivariable logistic regression analysis was conducted to assess the association of MS disease course, age, sex and bodyweight with risk of neutropenia in OCR-treated MS patients.
Results: Data on age, sex, bodyweight, and MS disease course were present in 3177of 15313 reports in total. Neutropenia occurred in 25/3177 of these cases. The outcome was rated as follows: hospitalized 17/25, life threatening 2/25, and other outcome 6/25. No deaths were reported. Multivariable logistic regression demonstrated that MS disease course was not associated, whereas younger age (0.909, 95%CI 0.875-0.944, p= 7.4105 x10^{-7}), lower bodyweight (0.961, 95%CI 0.935-0.988, p=0.005) and female sex (0.356, 95%CI 0.145-0.875, p=0.0124) were significant predictors of OCR-related neutropenia (Nagelkerkes R^2=0.17, n=3177).
Conclusion: We demonstrated that female sex, younger age and lower bodyweight are predictors of OCR- related neutropenia. Limitations of our study are associated with the design of the open data registry with several missing values and only a minimal clinical data set available as well as bias inherent to spontaneous reporting systems. The latter may account for both the overall lower rate of events as compared to the controlled trials and the higher rate of more severe outcomes.