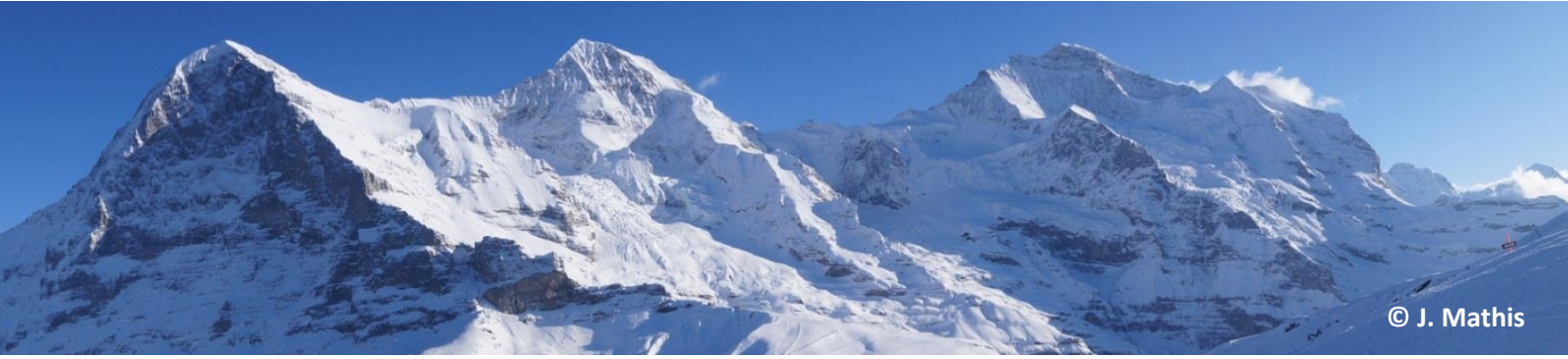
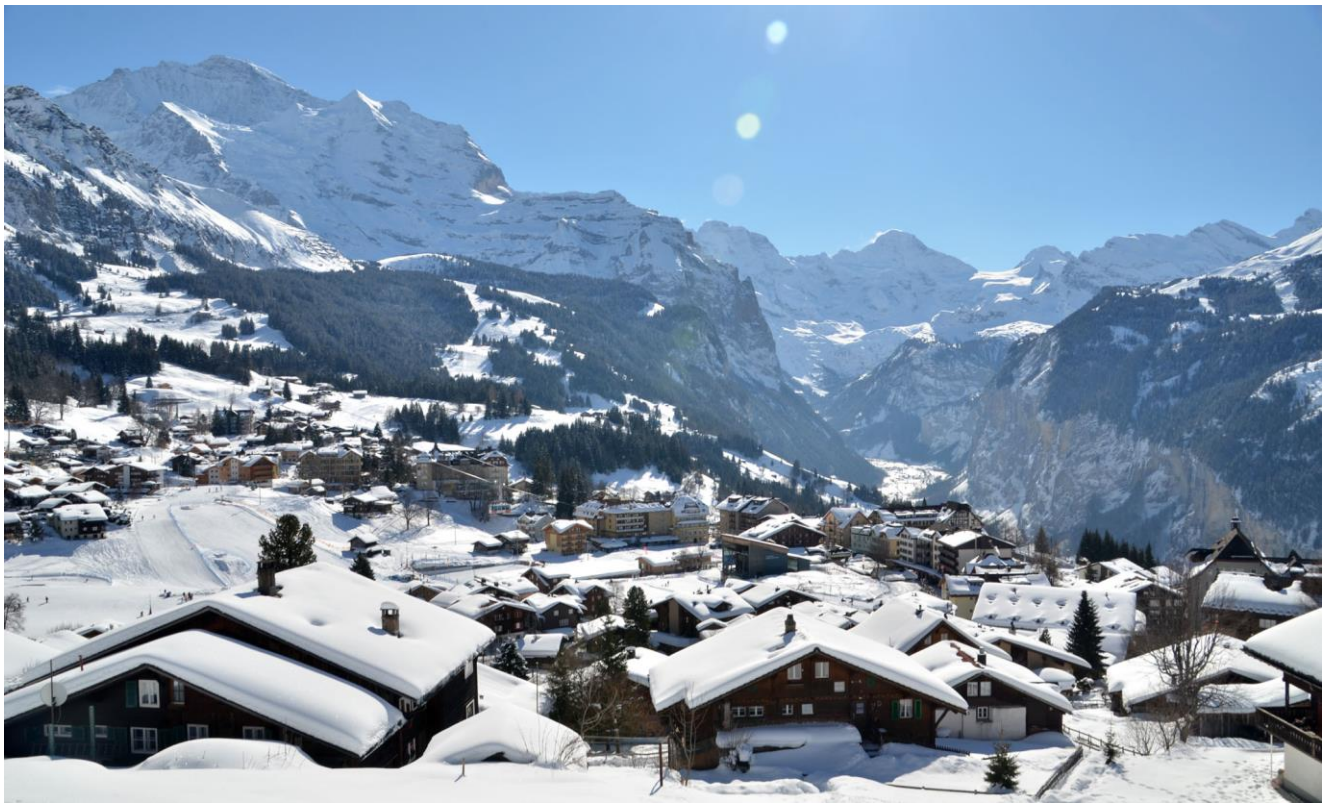


BENESCO

Bern Network Epilepsy Sleep Consciousness

4th Winter Research Meeting
Hotel Regina Wengen
2016 March 10 - 12



Contact: Dr. phil. Simone Duss, Sleep-Wake-Epilepsy Center, Department of Neurology, University Hospital Bern, Inselspital, simone.duss@insel.ch

Conference location & hotel: Hotel Regina, CH-3823 Wengen, www.hotelregina.ch

Dear participants of the 4th BENESCO Winter Research Meeting

We are pleased to conduct the fourth BENESCO Winter Research Meeting at the Hotel Regina in Wengen. The meeting is dedicated to the exchange of new research findings in the domain of Sleep, Epilepsy and Consciousness and also to the education of young researchers.

The meeting consist of six enriching and topical scientific sessions. On Thursday, the first session focuses on brain oscillations in health and disease and on sophisticated methods to detect them. Topic of the second session is insomnia, the most prevalent and still increasing sleep disorder in our society, and its treatment. In session three on Friday, the circadian sleep-wake regulation and regulation of other biological rhythms in animals and humans with mood disorders is highlighted. Session four focuses on the interlink between respiratory and cardiac disorders, a still neglected topic. Session five is dedicated to transcranial magnetic stimulation, an innovative tool in treating neurological and psychiatric disorders. Pain perception and regulation is the topic of the sixth scientific session on Saturday morning.

The two meeting highlights are the Young Scientists Session organized on Thursday night and the joint session of the BENESCO and CCLM (Center for Cognition Memory and Cognition of the University of Bern) on Saturday, completing this year's Winter Research Meeting.

We hope that you will gain new insights and enjoy the meeting.

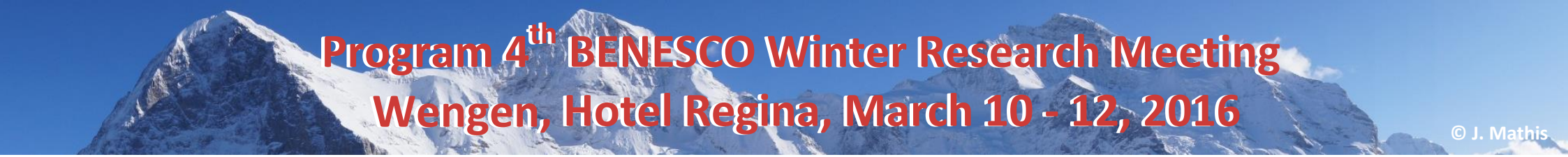
Prof. Dr. med. Claudio Bassetti
Chairman and Head
Neurology Department

Prof. Dr. med. Matthias Gugger
Chairman and Head Pulmonary Department, Director Teaching and Research

Prof. Dr. med. Johannes Mathis
Head Sleep-Wake-Epilepsy-Center

Prof. Dr. phil.
Antoine Adamantidis
Managing director Center for Experimental Neurology

Prof. Dr. med. Dr. sc. nat.
Kaspar Schindler
Managing director Sleep-Wake-Epilepsy-Center



Program 4th BENESCO Winter Research Meeting
Wengen, Hotel Regina, March 10 - 12, 2016

Overview meeting program

When			What		Session coordinators/chairs
Thursday	March 10	12:00-13:00	**Welcome lunch**		all
		13:00-13:15	**Welcome address**		Claudio Bassetti (Director BENESCO)
		13:15-15:00	**1st scientific session**	**Brain oscillations in health and disease**	Antoine Adamantidis (Experimental Neurology, Insel) Kaspar Schindler (Neurology, Insel)
		15:00-15:30	*Coffee break*		
		15:30-17:15	**2nd scientific session**	**Insomnia**	Thomas Müller (Psychiatry, Uni. Bern) Martin Hatzinger (Psychiatry, Solothurn)
		17:15-17:30	*Group picture*		all
		17:45-19:45	**Young scientist session**	**Data blitzes & posters: Young researchers present their scientific work**	all
		20:00	*Dinner*		all
Friday	March 11	07:00	*Breakfast*		
		08:00-09:45	**3rd scientific session**	**The circadian clock: Light, activity and psychiatric disorders**	Urs Albrecht (Chronobiology, Uni. Fribourg) Mauro Manconi (Neurology, Lugano)
		09:45-10:15	*Coffee break*		
		10:15-12:00	**4th scientific session**	**Lung, heart and brain: the interlink between respiratory and cardiac disorders**	Matthias Gugger (Pulmonary Medicine, Insel) Ramin Khatami (Psychosomatic Medicine, Barmelweid)
		12:00-17:00	*Individual lunch break and sports/social event*		
		17:00-18:45	**5th scientific session**	**Transcranial magnetic stimulation and neuropsychiatry**	René Müri (Neurorehabilitation, Insel) Dario Cazzoli (Perception & Eye Movement Laboratory, Insel)
		20:00	*Dinner, Mary's Café, Staubbachbänkli, Wengen*		
Saturday	March 12	07:00	*Breakfast*		
		08:30-09:45	**6th scientific session**	**Pain perception and regulation**	Thomas Nevian (Physiology, Uni. Bern)
		09:45-10:15	*Coffee break*		Johannes Mathis (Neurology, Insel)
		10:15-12:00	**Joint BENESCO-CCLM Session**	**Fantasy, Images and Dreams**	Fred Mast (Psychology, Uni. Bern) Daniel Erlacher (Sport Sciences, Uni. Bern)
		12:00-13:00	**Final discussion**		all
		13:00-14:00	*Farewell aperitif*		

Detailed meeting program – scientific sessions

Thursday, March 10

1st scientific session – Brain oscillations in health and disease

13:15-13:35	Fred Zubler	Top players ranking
13:35-13:55	Armand Mensen	Predictions of slow wave sleep
13:55-14:15	Luca Ratti	Sleep benefit in Parkinson Disease: the sleep, awake & move protocol
14:15-14:35	Laura Facchin	Optogenetic manipulation of cortical oscillations
14:35-14:55	Antoine Adamantidis	Causal Evidence for the role of REM sleep theta oscillations in memory consolidation

2nd scientific session – Insomnia

15:30-15:50	Christian Imboden	Aerobic exercise for insomnia and other symptoms of Depression
15:50-16:10	Cristina Zunzunegui	Differential effects of CBT for Insomnia (CBTi) in patients with and without depressive symptoms
16:10-16:30	Simone Duss	Online self-help program against Insomnia
16:30-16:50	Sarah Schiebler	ADHD and sleep disturbances: a study using actigraphy
16:50-17:10	Silvia Miano	Toward an unifying sleep related marker of prefrontal dysfunction in ADHD

Young scientist session – Data blitzes & posters: Young researchers present their scientific work

17:45-19:45 See abstracts next page

An aperitif will be served in parallel

20:00 Dinner

Friday, March 11

3rd scientific session – The circadian clock: Light, activity and psychiatric disorders

08:00-08:25	Urs Albrecht	Light and mood related behaviour in mice
08:25-08:50	Markus Schmidt	Division of labor and the circadian system: Role in energy conservation and sleep homeostasis
08:50-09:15	Ramin Khatami	Circadian and homeostatic modulations of parasomnic episodes and epileptic seizures" derived from a 40-hour nap protocol
09:15-09:40	Mauro Manconi	Perinatal depression: chronobiology, sleep related risk factors and light therapy

4th scientific session – Lung, heart and brain: the interlink between respiratory & cardiac disorders

10:15-10:35	Anne-Kathrin Brill	Patent foramen ovale and OSA: a prospective interventional study
10:35-10:55	Christian Horvath	Insight into OSA screening in bariatric patients
10:55-11:15	Stephany Fulda	Respiratory event associated leg movements
11:15-11:35	Marco Laures	Cerebral dynamics during respiratory maneuvers in healthy subjects and patients with sleep apnea
11:35-11:55	Thomas Horvath	Sleep disordered breathing in stroke (SNF-Project)

5th scientific session – Transcranial magnetic stimulation and neuropsychiatry

17:00-17:25	Dario Cazzoli	Non-invasive brain stimulation for rehabilitation of cognitive deficits after stroke: the case of neglect
17:25-17:50	Rahel Schumacher	Transcranial magnetic stimulation effects on aphasia recovery
17:50-18:15	Samir Suker	TMS in depression, clinical efficiency and mode of action
18:15-18:40	Yosuke Morishima	Control of effective connectivity through transcranial alternating current stimulation

Saturday, March 12

6th scientific session – Pain perception and regulation

08:30-08:55	Konrad Streitberger	Placebo in Pain Medicine
08:55-09:20	Uli Zeilhofer	The spinal cord in pain
09:20-09:45	Thomas Nevian	Cortical plasticity in neuropathic pain

Joint BENESCO-CCLM Session – Fantasy, Images and Dreams

10:15-10:40	Fred Mast	Mental imagery, predictions, and fantasy
10:40-11:05	Corinna Martarelli	Experimental approaches to the distinction between reality and fiction
11:05-11:30	Daniel Erlacher	Lucid dreaming
11:30-11:55	Sarah Schoch	Sleep, Dreams and Memory

End of Meeting

12:00-12:15	Closing words
12:15- 13:30	Farewell aperitif

Abstracts Young Scientist Session

ABSTRACT 1

A high-density polysomnographic picture of a case of NREM parasomnia

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[1] Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital (EOC) of Lugano, Switzerland

[2] Brain Function & Neuromodulation, Grenoble Institute of Neuroscience and Joseph Fourier University, Grenoble, France

Disorders of arousal (DOA) are NREM sleep parasomnias characterised by recurrent episodes of dissociated wake-sleep behaviours abruptly emerging from slow wave sleep. Their underlying mechanisms are still unknown. Aim of the study is to identify which brain areas are involved during DOA episodes and their pattern of activity. In a non-medicated otherwise healthy 22-year old male patient we recorded 14 DOA episodes during 2 V-PSG recordings (one by a 10-channel EEG montage, the other by a 256-channel HD-EEG montage). The pre-arousal period of each event was analysed by a time- frequency analysis (Morlet's wavelets), by a cortical source analysis; by a connectivity analysis (estimation of Granger's causality). In the pre-event period, time-frequency analysis showed an increase of delta (0.5-2 Hz) band power; source analysis demonstrated an increase followed by a decrease in delta band at right prefrontal cortex, followed by an increase of the same frequency band in right and left prefrontal and left temporal cortices compared to the baseline ($p<0.001$); connectivity analysis suggested bidirectional interactions among these three regions ($p<0.05$). We hypothesize DOA to be triggered by a failure of inhibition of delta activity starting at right prefrontal cortex, eventually resulting in the release of central pattern generators.

ABSTRACT 2

Localization of the epileptogenic zone using phase-amplitude cross-frequency coupling; comparing different approaches

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Fast oscillations, captured using depth and grid electrodes during pre-surgical evaluation of refractory epileptic patients, are the traditional biomarkers of epileptogenic brain areas. More recently, several studies reported that phase locked fast oscillations provide better alternatives for making decision about surgical resection [1-3]. Here we examined four different measures of phase-amplitude cross-frequency coupling, namely phase-locking value (PLV) [4], phase-locked high gamma (PLHG) [5], modulation index (MI) [4], and mean vector length (MVL) [4]. To assess the transient changes of these measures during initiation, propagation, and termination of epileptic seizures, a time-resolved approach was investigated through the segmentation of LFP signals into 1-sec windows.

Intracranial EEG recordings of epileptic patients who then underwent epilepsy surgery were analyzed. In patients with outcome Engel I, the time-resolved PLV showed significant increase during seizure initiation on the resected channels or their immediate neighboring channels, while the time-resolved PLV appeared in some non-resected channels in patients concurrent with bad outcome (Engel III and IV). Although the rest of measures could also show similar behaviors, the PLV measure was more robust. In fact the PLHG measure could not provide extra information with respect to PLV measure, as it essentially combines the information within gamma power and PLV. Furthermore MI is sensitive to high amplitude short duration events such as spikes, and should be measured on long windows (e.g. 10 sec) to achieve a more reliable estimation. Therefore MI is not a suitable measure for the time-resolved approach in the context of the current study, which necessitates short windows.

Keywords: Epileptogenic zone localization, fast oscillations, cross-frequency coupling.

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ABSTRACT 3

Phase-amplitude cross frequency coupling during different vigilance states provides hints to the underlying memory processes

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The importance of sleep stages on new memory formation has been justified through learning experiments on some species, by measuring resulting changes in consecutive REM and non- REM episodes [1]. Throughout sleep, most sensory inputs are blocked to some extent and brain retains higher chance of processing and maintaining of the acquired information during wakefulness. Phase-amplitude cross-frequency coupling (PAC) measures have been reported to increase following learning tasks in rodents [2, 3], monkeys [4], and humans [5]. More specifically, theta-gamma PAC have been linked to memory consolidation, nevertheless the precise underlying synaptic plasticity mechanisms remain elusive. We quantified phaseamplitude PAC using Modulation Index (MI) [3], which was estimated for a wide range of frequency bands and in different vigilance states of hippocampal LFP recordings of mice. Results show that theta phase significantly modulates slow and/or high gamma activities during awakeness, non-REM and REM stages. Specifically, MI between theta frequency (~7-8 Hz) and low gamma band (60-90 Hz) had higher values in all studied animals during awake stage. During REM sleep, in addition to theta-low gamma coupling, CFC also exists between theta and high gamma (120-160 Hz) in some hippocampal areas, and the frequencies of theta and low gamma are similar to the waking state. Furthermore, slow and high gamma oscillations are modulated in different phases of theta cycle. These findings can support the hypothesis of memory encoding and retrieval through different preferred phases, as well as through two distinct frequency bands of modulated gamma.

Keywords: Memory consolidation, sleep, phase-amplitude coupling.

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i-Sleep: Internet-based treatment of insomnia

Simone B. Duss[1], Antoine Urech[2], Tobias Krieger[2], Heidemarie Gast[1], Wolfgang Schmitt[1], Claudio L. Bassetti[1], Thomas Berger[2]

1 Bern University Hospital, Department of Neurology, Sleep-Wake-Epilepsy-Center, CH-3010 Bern

2 University of Bern, Department of Clinical Psychology and Psychotherapy, CH-3012 Bern

According to the current Swiss Health Survey, sleep complaints belong to the most frequently reported troubles. 25% of the interviewees suffered from sleep troubles and reported decreased life quality and higher psychological stress. In addition, 8 of 100 people indicated to take medication to improve their sleep.

Insomnia is defined as difficulties to fall asleep, maintain sleep or early awakening despite adequate opportunity and circumstance to sleep, associated with day time impairment or stress. Insomnia is discussed as a precursor for major depression episodes, and its progression is often chronic. Early diagnosis and adequate treatment is therefore important. According to the clinical guidelines for management of insomnia, supported by the American Association of Sleep Medicine, cognitive behavioral therapy (CBT) corresponds to the gold standard. If possible, there is consensus that short-term hypnotic treatment should be supplemented with CBT. However, often adequate treatment options are missing or sparse, general practitioner and psychiatrists are insufficiently informed and patients weight short-term costs higher than long-term benefits. Therefore, more and more internet-based CBT programs consisting of different treatment modules (such as sleep hygiene, stimulus control, sleep restriction, relaxation and cognitive restructuring) to improve insomnia are developed. First meta-analyses corroborate their effectiveness. Since people nowadays lack time, a very relevant factor is efficiency, i.e. short and effective internet-based interventions are of interest.

In the present trial, we therefore compare effectiveness of a multicomponent internet-based cognitive behavioral self-help program (iCBT-I) versus the single internet-based module “sleep restriction” to treat insomnia. In face-to-face CBT-I interventions, sleep restriction (i.e., shortening the time allowed to spend in bed) has proven to be one of the most effective therapy components for insomnia.

We recruit patient with diagnosed insomnia relying on the international classification system of sleep disorders (ICSD-3) without psychiatric comorbidities. Participants undergo assessments before and after the interventions (self-help multicomponent program or self-help sleep restriction). Both internet-based interventions take 8 weeks. A 6-month follow-up assessment will also be conducted. The primary outcome is the pre-post change in sleep efficiency, calculated as the percentage of total sleep time over total time in bed before and after the intervention. We also recruit a waiting control group of insomniac patients that receive no internet-based interventions but only care as usual during the first eight weeks. We hypothesize that sleep restriction is as effective as the multicomponent iCBT-I intervention and that both active interventions improve sleep efficiency and insomnia complaints to a higher degree than care as usual.

ABSTRACT 5

Optogenetic Modulation Of Sleep Slow Wave After Focal Ischemic Stroke

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Introduction: Stroke is one of the leading causes of death worldwide with very limited treatment options. Sleep-wake disturbances are frequent after stroke and they are linked with poorer rehabilitation and long-term outcomes. Patients with stroke injury are reported to have abnormal sleep architecture with significantly reduced slow wave sleep (SWS) and rapid eye movement (REM) when compared with normal subjects. Stroke induces delayed neuronal death in human and in animals models in the hippocampus, but can also affect the cortex, where the inhibitory neurons are crucial in regulating the balance of excitation and inhibition, plasticity and functional architecture of cortical circuits. During sleep, cortical neurons exhibit a characteristic oscillating activity about once every second from a hyperpolarized downstate to a depolarized upstate. Within the downstate these neurons are almost silent whereas during the upstate neuronal firing rates can be as high as in quiet wakefulness. Several studies demonstrated that sleep plays a key role in the reorganization of neuronal connections and neuroplasticity and has a protective effect during the recovery period after stroke.

Hypothesis: Sleep-like oscillations may have a protective effect after ischemic stroke. We use optogenetic techniques combined to in vivo electrophysiology to specifically stimulate neurons within the forelimb somatosensory cortex inducing slow sleep-like oscillations to promote a positive effect on the motor activity previously affected by the stroke.

Methods: In order to induce stroke in the experimental group of animals, Intraluminal Middle Cerebral Artery Occlusion (MCAO) model was performed in mice. AAV2 DIO-EF1-ChR2-EYFP (VGAT-ChR2), AAV2 DIO-EF1-ArchT-EYFP (VGAT-ArchT), AAV2 DIO-EF1-EYFP (YFP, control), CamkII-ChR2-EYFP (CamKII-ChR2), CamkII-ArchT-EYFP (CamkII-ArchT) and CamkII-mCherry (mCherry, control) adeno-associated viruses (AAV) were injected into the layer V of the forelimb somatosensory cortex of Tg(VGAT)-IRES::Cre and wild type mice, respectively. The genetic targeting was assessed by immunohistochemistry staining. Transduced animals were chronically implanted with optical fibers, tetrodes directly above cortical layer V for optogenetic activation and simultaneous electrophysiological recordings and polysomnographic recordings. Optical stimulation provides either the cortical excitation or inhibition, depending on the experimental condition. Local Field Potential (LFP) recordings of the interested neuronal area were performed as well as several stimulation protocols, with various modalities, frequencies and time durations.

Results: Immunohistochemistry analysis confirmed the presence of transfected cells within the layer V, forelimb somatosensory cortex. YFP and mCherry (controls) were expressed within the soma while ChR2, ArchT, CamkII-ChR2 and CamkII-ArchT were preferentially found along the cell

membrane revealing the projections within the neocortex layers, striatum and internal capsula. Cortical LFPrecodrings from wild type mice injected with CamkII-ChR2 and CamkII-ArchT and from VGAT::Cre transgenic animals injected with ChR2 and ArchT showed signal deflections immediately after the light stimulus induction, suggesting a stimulus-dependent response of the cortical circuits. In particular, we found that 5-Hz light pulses induced responses in both ChR2 and CamkII-ChR2 injected animals. 1, 2, 5 sec continuously illumination had similar effects in VGAT-ArchT and CamkII-ArchT transfected animals. LFP and spike analysis during the 500 ms optical silencing in CamkII-ArchT animals showed a brief modulation of the brain activity similar to a down-state, that correlates with a quiescent period from some of the recorded unit. In YFP and mCherry no response was observed (data not shown).

Conclusion: Preliminary data show that all the injected virus types successfully targeted the layer V neuronal cells of the somatosensory cortex in both transgenic (Cre-dependent construct) and wild type (CamKII construct) mice. Among all the stimulation protocol tested, 500ms silencing of Excitatory Pyramidal neurons induced "down" states of the neuronal network detected in LFP trace as well as a pause in the single cell spike activity. This represents the first step in the modulation of sleep-like oscillation.

ABSTRACT 6

Optogenetic stimulation of the Centromedian Thalamus promotes wakefulness from Non-Rapid Eye Movement Sleep (NREM)

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Background
The high amplitude low frequency oscillations of the EEG seen during natural sleep originate from thalamocortical reverberations. However the mechanism behind the initiation of these oscillations is not known nor is the mechanism by which consciousness is regulated. The centromedian thalamus (CMT) is implicated in the control of consciousness of both general anaesthesia and natural sleep and may be an important hub for sensory processing.

Methods
Adult male C57Bl6 mice were transfected with AAV2-CamKII-ChR2-EYFP or AAV2-CamKII-EYFP (as control) in the centromedian thalamus or lateral thalamus (VB) and implanted 4 weeks later with fibre optics and EEG/EMG electrodes for optogenetic recording. Stimulation was performed during NREM. Midline thalamic LFPs were recorded using a 16-channel shank electrode in freely behaving naturally sleeping mice. Histology was performed on 40µm brain sections and viewed with fluorescence microscopy.

Results
Optogenetic stimulation of the CMT lead to rapid arousal (<2s) from NREM at 10Hz, 20Hz and 1s stimulations with a concurrent entrainment of the EEG with a high fidelity to the stimulation. Stimulation of VB did not result in reduced time to wakening. Local field potential recording from the midline thalamus showed a phase advancement of the CMT over other thalamic areas (-0.2π) and the neocortex immediately after the onset of NREM, in the delta band (1-5Hz).

Conclusions
The CMT may act as a central hub for regulating cortical arousal, a feature which is not shared by the lateral thalamus. Furthermore, the phase advancement over other thalamic nuclei during NREM implicates it as a driver of delta, the predominant oscillation during NREM and may therefore play a significant role in the onset and maintenance of sleep as well as wakefulness. Future work is aimed at elucidating the chemical nature of the transmission to the CMT, which controls its activity.

ABSTRACT 7

Hypothalamic feedforward inhibition of thalamocortical network controls arousal and consciousness

Carolina Gutierrez Herrera[1,2], Marta Carus Cadavieco [3], Mojtaba Bandarabadi[1], Kaspar Schindler[1], Alexey Ponomarenko[3], Tatiana Korotkova[3] & Antoine Adamantidis[1,2, 4]

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2 Douglas Institute, Department of Psychiatry, McGill University, Montreal, Canada.

3 Leibniz Institute for Molecular Pharmacology (FMP)/ NeuroCure Cluster of Excellence, Berlin, Germany.

4 Department of Clinical Research (DKF), University of Bern, Bern, Switzerland.

In mammals, during non-rapid eye movement (NREM) sleep, the electroencephalogram (EEG) activity shows typical signs of brain activity that include a predominant slow wave (< 1 Hz) associated with delta oscillations (1-4 Hz) and spindles (11-15 Hz) 1-3. Synchronous synaptic activity in the thalamocortical network is believed to generate these low-frequency oscillations and that are modulated by inhibitory inputs from the thalamic reticular nucleus (TRN). Whether TRN cells integrate sleep-wake signals from subcortical circuits remains unclear. We identified a monosynaptic GABAergic connectivity between the lateral hypothalamus and the TRN (LHGABA-TRNGABA), transmission that exerts a strong inhibitory control over TRN neurons. We found that optogenetic activation of this circuit recapitulated state-dependent changes of TRN neuron activity in behaving mice and induced rapid arousal during NREM, but not REM, sleep. During deep anaesthesia, activation of this circuit induced sustained cortical arousal. In contrast, optogenetic silencing of LHGABA-TRNGABA transmission increased the duration of NREM sleep and amplitude of delta (1–4 Hz) oscillations. Collectively, these results demonstrate that TRN cells integrate subcortical arousal inputs selectively during NREM sleep and may participate in sleep intensity.

Keywords: Sleep, Reticular thalamic nucleus (TRN), lateral hypothalamus, anaesthesia.

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ABSTRACT 8

Isolation and characterization of hypocretin-reactive CD4+ T cells in narcoleptic patients

Ulf Kallweit[2], Daniela Latorre[1], Eric Armentani[1], Mauro Manconi[3], Ramin Khatami[2], Claudio L. Bassetti[2], Federica Sallusto[1]

[1]Center of Medical Immunology, Institute for Research in Biomedicine, Università della Svizzera Italiana, Bellinzona, Switzerland;

[2]Neurology Department, University Hospital, Bern, Switzerland; 3Ospedale Regionale di Lugano (EOC), Lugano, Switzerland.

Narcolepsy-cataplexy is a rare sleep-wake disorder that manifests in genetically predisposed individuals and is caused by the selective loss of neuronal cells of the posterior hypothalamus that produce the neuropeptide hypocretin (HCRT). Genome-wide association studies showed a strong association with HLA DQB1*06:02 and other genes involved in immune modulation, such as T cell receptor alpha and OX40L, supporting the notion that narcolepsy is a T-cell-mediated autoimmune disease. However, attempts to identify hypocretin-specific T cells in narcoleptic patients have been so far unsuccessful. In this study we combined antigenic stimulation, T cell cloning, and TCR deep sequencing to characterize the T cell response in HLA-DQ0602-positive donors with a diagnosis of narcolepsy/cataplexy. T cells were isolated from blood and, when available, CSF, and either directly stimulated with overlapping peptides covering the entire 131 aa-long hypocretin precursor protein (prepro-hypocretin) or expanded polyclonally with mitogen and IL-2 in microcultures to generate T cell library that were subsequently interrogated for reactivity against prepro-hypocretin peptides as well as putative cross-reactive antigens. Hypocretin-reactive CD4+ T cell clones were identified in all patients analyzed so far (n=5), but not in HLA-DQ0602-positive control donors. The clones use different TCR $\alpha\beta$ and recognize several regions of the prepro-hypocretin protein. Next-generation TCR sequencing was also performed on total T cells from blood and CSF in order to gather information on narcoleptic patients' TCR repertoire, to search for shared clonotypes, and to define expansion and localization in vivo of hypocretin-reactive T cell clones. Although the contribution of hypocretin-reactive T cells in the pathogenesis of narcolepsy remains to be demonstrated, our data demonstrate for the first time the existence of expanded hypocretin-reactive CD4+ T cells in narcoleptic patients.

ABSTRACT 9

Chronic pain blocks the induction of NO-dependent LTD in mouse ACC

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Synaptic plasticity, i.e. the modification of synaptic strength is thought to be a cellular mechanism for learning and memory as well as the cause for many pathological conditions of the nervous system including chronic pain. Chronic pain is a health problem with high prevalence. The perception and evaluation of pain involves several brain regions comprising the "pain matrix". The *Anterior Cingulate Cortex* (ACC) is an essential part of the pain matrix and it is especially important for the emotional aspects of pain.
We studied spike-timing dependent long-term depression (tLTD) at synapses onto layer 5 pyramidal neurons in the ACC in adult mouse. Pairing of post- and presynaptic activity (post leading pre by 25 ms) resulted in synaptic depression in control animals. Strikingly, if mice are subjected to chronic constriction injury (CCI) of the sciatic nerve (an animal model for studying chronic neuropathic pain) the induction of tLTD is impaired. Investigation of the underlying molecular mechanism showed that the induction of tLTD depends on postsynaptic calcium-influx through NMDARs triggering the synthesis of nitric oxid (NO); mGluR and endocannabinoid signalling is not involved. Bath application of a NO-donor induced LTD in control and CCI animals suggesting that neuropathic pain only affects the cellular mechanisms for the induction but not the expression of tLTD. We further analysed the role of NMDARs in tLTD. We found that the induction of tLTD is blocked by inhibiting NMDARs containing the subunit *GluN2B*. Moreover, we discovered that in the CCI condition the NMDAR:AMPAR ratio is increased and that the contribution of *GluN2B* to the total NMDAR-mediated synaptic current is reduced. Our results suggest that, in the ACC, neuropathic pain is accompanied by an exclusion of *GluN2B*-containing NMDAR from the synapse. This molecular switch in the NMDAR subunit composition might be the cause for the impairment of tLTD and could be a potential target for novel treatment strategies for neuropathic pain.

ABSTRACT 10

Predictive modeling of post-surgical outcome in epilepsy treatment

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Resective surgery of the epileptogenic zone is one of the last resorts for epilepsy patients who cannot be treated successfully by pharmacological means. Since in many cases this zone cannot be extracted by visual inspection of the raw intracranial EEG data, one may alternatively construct a statistical model of the EEG spatio-temporal dynamics. These models can then be used to predict the evolution of such dynamics under different, simulated brain resection paradigms (that is, simulated manipulations of signals from one or more EEG channels).
For several patients with different surgical outcomes (Engel classes I and IV), we generated spatio-temporal predictive models (Bayesian networks mixed by a Hidden Markov Model) and analyzed their predictions on seizure evolution. We simulated the resection of those EEG channels that were truly resected during the surgery and compared the results to the simulated resection of random sets of channels.
In six of the seven class I patients, we could confirm the clinical significance of the truly resected channels, by observing a significantly and massively reduced probability of entering the seizure state. In the remaining case, reduction was insignificant. On the other hand, for two of the three class IV patients reduction was neither massive nor significant, where as in the remaining case reduction was unintentionally massive and significant.
In summary, for eight out of ten cases, our model confirmed the (ir)relevance of the truly resected channels for clinical outcome. Hence, our results pave the way for the development of objective analysis tools in future epilepsy research.

ABSTRACT 11

Encoding of food intake and arousal by GABAergic neurons in the lateral hypothalamus

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Introduction: In mammals, the sleep-wake cycle and feeding behaviors are very conserved processes engaging a broad range of brain regions. The hypothalamus has a key role in the integration and regulation of these two behaviors as it receives information from intra- and extra hypothalamic networks. Here we investigate how GABAergic cells in the lateral hypothalamus (LH_{GABA}) modulate food intake and arousal.

Methods: To selectively manipulate neuronal activity we targeted expression of the light-sensitive cation channel channel-rhodopsin 2 (ChR2) to LH_{GABA} cells in the lateral hypothalamus in tg(*vgat)::cre* mice. To deliver laser stimulations we chronically implanted mice bilaterally with optical fibers. For population calcium imaging the LH_{GABA} neurons were transduced with the fluorescent calcium sensor GCaMP6s. Imaging was performed through a gradient refractive index lens implanted into the hypothalamus with an integrated mini fluorescence microscope. For both, stimulation experiments and imaging, cortical EEG and EMG were obtained to score sleep states. Additionally, the animals were filmed and their behavior was scored.

Results: Optogenetic stimulation of LH_{GABA} cell bodies at 1 or 20 Hz for 10 s, as well as 1 s continuous light during NREM sleep elicited rapid arousal of the animals. Interestingly, stimulation at 20 Hz or continuous illumination, but not at 1 Hz, initiated food intake immediately after arousal. When the neurons were stimulated during wakefulness only stimulation at 20 Hz or continuous illumination initiated food intake. In a semi-chronic, state-invariant protocol, where 10 s of stimulation at 20 Hz were delivered every minute, both food consumption and the number of feeding events were higher than in controls. *In vivo* calcium imaging revealed a peak of cellular calcium transients when animals started to eat. Over the time course of the feeding event the calcium transients decayed back to the level observed for locomotion (wakefulness). Furthermore, during NREM sleep and immobility the calcium transients were lower than during movements and active behaviors.

Conclusion: These findings showed that LH_{GAB} cells control both sleep and metabolic function. Our results raise the possibility that LH_{GABA} can encode behaviors by distinct activity thresholds, which awaits further investigations.

ABSTRACT 12

Role of REM sleep and melanin concentrating hormone in the neuroprotection effect of sleep deprivation pre-ischemia preconditioning

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Background: It has been shown that REM sleep reduction in the acute phase after stroke is related to poor outcome. In this study, we used Sleep deprivation (SD) as a form of ischemic preconditioning to investigate the role of REM sleep on ischemia. Moreover, our previous microarray study showed an increase of Melanin Concentrating Hormone (MCH), which is a neuropeptide involved in the regulation of REM sleep performed in SD pre-ischemia animals.
The objectives of the study are: firstly, to define the role of REM sleep in functional recovery after ischemia and thus may be used as a prognostic marker. Secondly, whether MCH is associated with the pathophysiology of stroke and with the beneficial effect elicited by SD.

Methods: Sprague-Dawley rats were assigned to four experimental groups: (i) SD_IS: SD performed before ischemia; (ii) IS: ischemia without previous SD; (iii) SD_Sham: SD performed before sham surgery; (iv) Sham: sham surgery without SD. Electroencephalogram (EEG) combined with electromyogram (EMG) were recorded to evaluate changes in sleep. The time course of the precursor of MCH (Pmch) and its receptor MCH1 receptor (Mchr1) were performed at 4,12 and 24 hours and 3,4 and 7 days following ischemic surgery in the lesioned and contralateral hemispheres by quantitative Real-time qRT-PCR. The infarct size was assessed by cresyl violet staining.

Results: REM sleep was significantly increased in the SD_IS (25%) and SD_Sham (30%) groups until 2 days after interventions compared to the baseline and all other groups. Conversely, REM was markedly reduced in the IS group (60%) 24h after interventions, when compared to baseline.
Both groups that underwent ischemia (SD_IS and IS) showed a significant increase of Pmch and Mchr1 during the acute phase of stroke (4h to 24h) and in both hemispheres relative to the sham group. Furthermore, Pmch was still increased only in SD_IS after 3 and 5 days and in the lesioned hemisphere. Infarct volume was significantly reduced in SD_IS group compared to IS group at 12h ($p = .0013$); 5 ($p = .0001$) and 7 days ($p = .0019$) after ischemia, no reduction was observed at 24h and 3 days.

Conclusion: These results indicate that the increase of REM sleep influences infarct volume positively, suggesting that REM may be clinically used as a prognostic marker to identify a subgroup of patients with different outcomes. Additionally, this is the first study, which observed and associated MCH in ischemic context. Since MCH increases the quantities of REM, it would be interesting to determine if MCH agonists could be useful in the treatment of stroke patients.

ABSTRACT 13

Gamma aminobutyric acid receptor antagonist promotes functional neurological recovery after permanent distal middle cerebral artery occlusion in rats

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Background: Although stroke is one of leading causes of permanent disability, no successful treatments are available for promoting recovery in stroke patients. Gammaaminobutyric acid receptors (GABAAR), responsible for tonic neuronal inhibition, are elevated in the peri-infarct region and may antagonize the neuronal plasticity required for functional recovery after stroke. The objective of the study is to determine the safety and effects on functional recovery after stroke of potent and competitive selective GABAAR antagonists on rats that underwent middle cerebral artery occlusion.

Methods: Sprague-Dawley rats, randomly assigned either to sham surgery or permanent distal middle cerebral artery occlusion, were subjected to twice-a-day treatment with the α 5- GABAAR antagonist S44819, administered at two doses, 3 and 10 mg/kg, respectively, or vehicle. S44819 was orally administered over 28 days starting at day 3 post-stroke. Rats were sacrificed after 2 weeks of washout at day 45 post-stroke. Single pellet reaching (SPR) tests were performed for assessing functional recovery after the stroke at 10, 17, 24, 31, 38 and 45 days post-surgery. Infarct volume was evaluated by cresyl violet staining.

Results: Rats receiving 10 mg/kg of S44819 showed a significantly better performance in SPR rests than rats receiving 3 mg/kg of S44819 or vehicle. Notably, functional recovery in rats receiving 10 mg/kg of S44819 was fast, reaching a plateau effect already 10 to 17 days post stroke. Infarct volume did not differ between groups.

Conclusion: These results indicate that a high dosage of chronically administered S44819 improves functional neurological recovery post-stroke in rats, suggesting the utility of this GABAAR antagonist for stroke treatment in human patients.

ABSTRACT 14

The impact of chronotypical variations in alertness on the spatial deployment of visual attention and its physiological correlates

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Attention is a complex cognitive function that is crucial in everyday life. An influential model postulates that non-spatial (e.g., alertness) and spatial aspects of attention are governed by two distinct, yet interacting, cortical networks in the human brain. However, to date, the interactions between non-spatial and spatial attentional aspects are poorly understood.

The aim of the present study was to further elucidate these interactions, by manipulating the alertness level in healthy participants, and assessing the impact of this manipulation on spatial attentional aspects both on a behavioural and on a physiological level. Participants' alertness level was manipulated through the (a)synchronicity between their chronotype and the time of the day. Hence, participants were tested both during their optimal and their non-optimal time of the day. In each session, participants' alertness level was assessed both subjectively and objectively. On a behavioural level, the spatial deployment of visual attention was assessed by means of a free visual exploration task, with concurrent eye movement recording. On a physiological level, the excitability of the left and the right posterior parietal cortices (PPCs) – two critical nodes of the network governing spatial attention – was directly assessed by means of a transcranial magnetic stimulation (TMS) twin-coil approach.

The results of the subjective and the objective alertness tasks showed a significantly decreased level of alertness during the non-optimal compared to the optimal time of the day. Moreover, the spatial deployment of visual attention, in terms of the spatial distribution of visual fixations, differed significantly during these two time points. The results at the non-optimal time of the day were characterised by a rightward shift of the fixation distribution in the central part of the visual exploration field, as well as by a bilateral narrowing in the periphery of the latter. Furthermore, the cortical excitability of both PPCs significantly differed when measured at the two time points, and there were significant correlations between physiological and behavioural measures.

The results of the present study show that the manipulation of non-spatial attentional aspects, such as alertness, can affect the spatial deployment of visual attention, and these effects are measurable both on a behavioural and on a physiological level. The results are discussed within the context of current models of visual attention, and possible implications for healthy individuals and clinical populations are considered.

ABSTRACT 15

Fast orexin/hypocretin activation during sensory stimulus evoked sniffing

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Lateral hypothalamic orexin (hypocretin) neurons have widespread projections throughout the brain and interact with arousal and cardiorespiratory systems. Disturbances in orexin signaling result in narcolepsy with cataplexy in rodents, dogs and humans and thus are key for normal arousal and sleep/wakefulness. While the effects of fast activation and inhibition of orexin-containing neurons on sleep/wake states has been strikingly demonstrated using optogenetic tools, it is less clear what role orexin neurons play for fine adjustment of arousal to environmental stimuli. Here we show fast increase in orexin calcium-signals upon sensory stimulation in vivo. Our data indicates that orexin neurons may modulate sensory stimulus evoked sniffing - a behavior shown to allow increased sampling of odorant cues during high vigilance states and exploratory behavior. We also show that optogenetic activation of orexin neurons results in increased sniffing within milliseconds, indicating that their activity is sufficient to trigger sniffing behavior.

Sleepiness & Driving

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Objective: We recently described that after sleep deprivation spontaneously perceived sleepiness (SPS) is accurate in a driving simulator but not in ~30% of individuals in the maintenance of wakefulness test (MWT) condition [1]. In a second step we investigated now, whether: (1) SPS could more accurately predict sleepiness than the Karolinska Sleepiness Scale (KSS) when comparing both with the first sleep fragment (SF) in the driving simulator and the MWT, (2) SPS could more accurately assess sleepiness than driving performance parameters when compared to the first SF.

Methods: Twenty-four healthy individuals (20-26y) underwent a 1h-driving simulator and a 40 min-MWT, both before and after one night of sleep deprivation (described in more detail elsewhere [1]). For each trial, the KSS was assessed for the moment before the trial and retrospectively for the trial duration. We measured the latency to the first SF, the latency to the first off-road event (Foff) and the number of off-road events per hour (off/h).

Results: Before and after sleep deprivation in the MWT, SPS detected the occurrence of ≥ 1 SF worse (71% sensitivity/ 58% specificity) than if both KSS values were ≥ 7 (100% sens. / 83% spec.). In the driving simulator, SPS was more sensitive (100% / 26%) but less specific than if both KSS values were ≥ 7 (92% / 67%). Since SFs occurred only after sleep deprivation, SPS or driving parameters have been compared with it after sleep deprivation only. The latencies to SPS (ρ=.823, p<0.001) and Foff (ρ=.877, p<0.001), and off/h (ρ=-.908, p<0.001) strongly correlated with the latency to the first SF. SPS (Median,Md= 5 min 42s) and Foff (Md= 9 min 48s) always preceded the first SF (Md= 47 min 29s).

Conclusions: In the MWT, SPS detected SFs less sensitive and specific than the KSS. In the driving simulator, SPS was more sensitive but less specific than the KSS. SPS or Foff or off/h showed strong and significant correlations with the latency to the first SF. However, SPS seemed to be the earliest indication of sleepiness and the most sensitive parameter to assess sleepiness in a driving condition. The lower specificity of SPS compared to the KSS may also be explained by the presence of shorter (< 3 sec) and therefore undetected SF. Following SPS, driving performance started to be impaired. It appears that SPS for fitness-to-drive should be evaluated in the driving simulator since it significantly differs to the MWT [1].

[1] Schreier et al. Sleep Med 2015

ABSTRACT 17

White matter lesion burden and sleep disordered breathing in acute stroke

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Introduction: The frequency of sleep-disordered breathing (SDB) is high in acute stroke patients. Few small studies suggested that stroke patients with SDB may present an increase in cerebral white matter lesions (WML) of presumed microvascular origin, which are known to be associated with a worse outcome.

The purpose of this study is to assess prospectively and systematically the relationship between the extent of WML and SDB in patients with acute ischemic stroke or transitory ischemic attack (TIA).

Patients and methods: All patients with MRI and nocturnal polysomnography within 14 days after ischemic stroke or TIA were selected from the SAS-CARE cohort (SDB in TIA/Ischemic Stroke and Continuous Positive Airway Pressure Treatment Efficacy; NCT01097967) from two centers, Bern and Lugano. SDB was defined as Apnea-Hypopnea-Index (AHI) ≥10. White matter lesions on T2/FLAIR imaging were graded visually by Fazekas classification and also assessed semi-automatically.

Results: We included 98 patients, 65 (66%) of whom had SDB. WML were significantly higher in the SDB-group (p=.002 for WML volume, p=.001 for periventricular and deep WML according to Fazekas). WML severity and AHI correlated significantly (rs=.321, p=.001 for WML volume; rs=.311, p=.002 for periventricular and rs=.290, p=.004 for deep WML). Multivariable analysis with adjustment for age, hypertension, smoking and diabetes showed that periventricular (p=.023) and deep (p=.035) WML were independently associated with sleep apnea.

Conclusion: Stroke/TIA patients with SDB have significantly more WML than those without SDB. Moreover, SDB is independently associated with periventricular and deep WML.

ABSTRACT 18

Virtual Reality-Based Attention Bias Modification Training for Social Anxiety: A Feasibility and Proof of Concept Study

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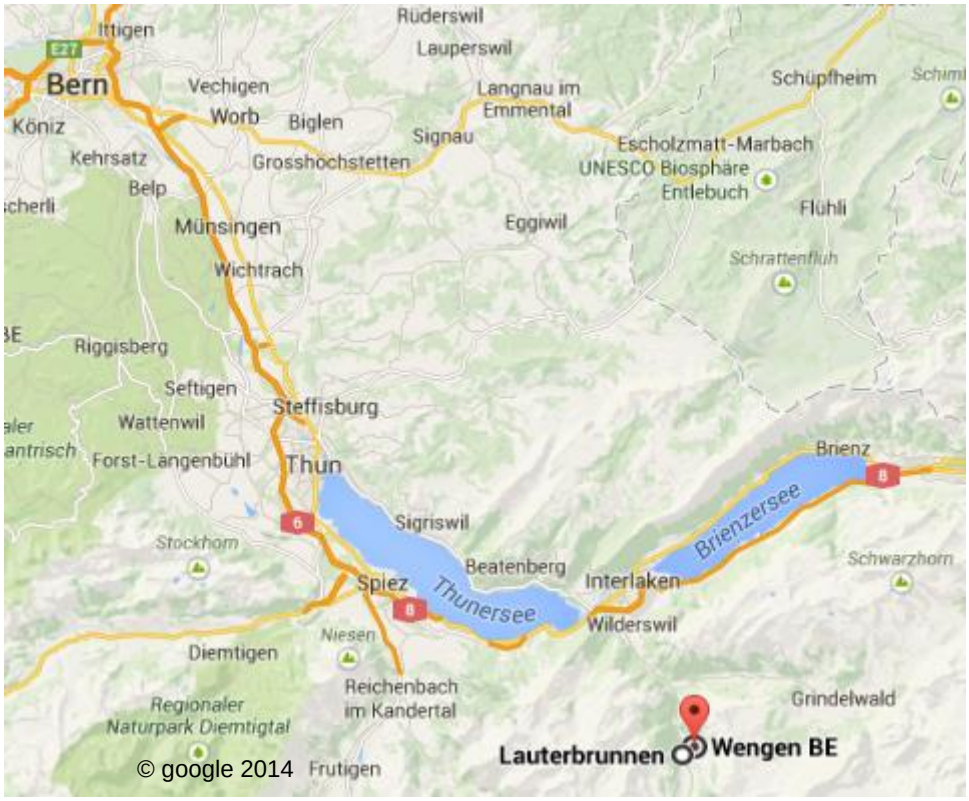
Attention bias modification (ABM) programs have been considered as a promising new approach for the treatment of various disorders, including social anxiety disorder (SAD).
However, previous studies yielded ambiguous results regarding the efficacy of ABM in SAD. The present proof-of-concept study investigates the feasibility of a newly developed virtual reality (VR)-based dot-probe training paradigm. It was designed to facilitate attentional disengagement from threatening stimuli in socially anxious individuals (*N* = 15). The following outcomes were examined: (a) self-reports of enjoyment, motivation, flow, and presence; (b) attentional bias for social stimuli; and (c) social anxiety symptoms. Results showed that ABM training is associated with high scores in enjoyment, motivation, flow, and presence. Furthermore, significant improvements in terms of attention bias and social anxiety symptoms were observed from pre- to follow-up assessment. The study suggests that VR is a feasible and presumably a promising new medium for ABM trainings. Controlled studies will need to be carried out.

General Information

Meeting venue

By train: from Bern via Interlaken Ost, to Wilderswil, Lauterbrunnen, Wengen

By car: from Bern to Wilderswil (car park) or Lauterbrunnen (car park) then by train to Wengen



Accommodation

Hotel Regina, CH-3823 Wengen; www.hotelregina.ch; phone: +41 33 856 58 58; individual booking by e-mail to reservation@hotelregina.ch.

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