UNIVERSITÄT BERN

Interfaculty Research Cooperation:
Decoding Sleep

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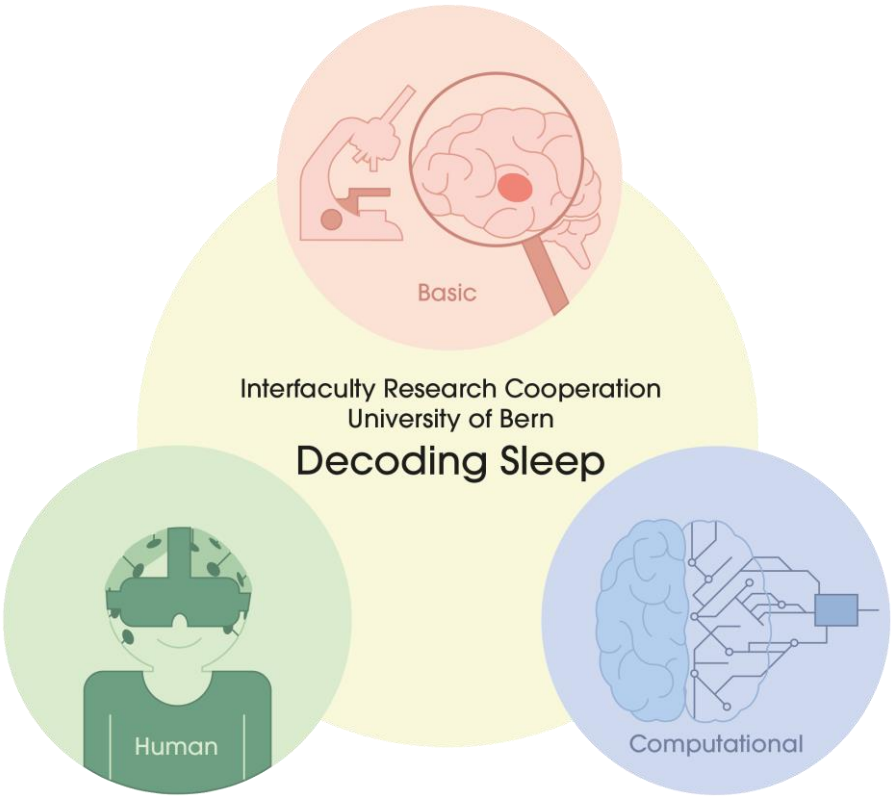
Decoding Sleep
From Neurons to Health and Mind

Final Report / Year 4 Report – 20. January 2022



Director: Prof. Dr. med. Claudio Bassetti
Co-Director: Prof. Dr. Fred Mast

www.sleep.unibe.ch

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A. SCIENTIFIC PART

A1. Short Summary

We will continue to develop the field of sleep research across different faculties at the University of Bern, and to further exploit interdisciplinary connections which ultimately lead to knowledge gain, innovation, and improve the societal impact. With the beginning of the third year we started a pruning process to reduce the number of groups and projects to identify the strong core of the consortium that will be able to successfully carry the IRC network into the future.

The fourth year of the IRC has been characterized by the following six achievements:

1) most experiments of the **original projects** (n=13) could be completed;
2) **Two new projects** launched in summer of 2019 have been developed successfully.
3) new **interdisciplinary collaborations were** created with the appointment of four new PhD students for projects on animal models of narcolepsy and schizophrenia and studies in patients with narcolepsy, epilepsy and coma bridging the three main clusters (basic, human, computational) of the IRC consortium.
4) the new platform **NeuroTec** (https://www.neuro-tec.ch) was opened in September 2021, and it will make the exploration of novel technologies in clinical sleep research available and more efficient.
5) the **Swiss Sleep House Bern**, was approved by the Insel-Gruppe in November 2021 and will be launched in summer 2022;
6) 6 PI (three of them females) of the IRC consortium were **promoted academically** (habilitation, assistant/associate professorship, full professorship). One of these is a new joint professorship at the Medical and Science Faculties (A. Tzovara).

Most groups are still impacted by the consequences of the Covid-19 pandemic and the severe delays caused by the initial lockdown in 2020 were not fully compensated. Coupled with the initial hiring phase and individual challenges faced by different groups, several projects need additional time to guarantee a successful completion. The majority of research groups has sufficient funds remaining so that a cost-neutral extension will cover the costs. Those funds were not saved for strategic means, but they were rather accumulated because of the above-mentioned delays. Please also refer to our letter from December 13, 2021 which explains in detail the situation for each project, the remaining funds, and the additional time needed.

Over the last four years the IRC strengthened the existing research in neurology and neuroscience and inspired the development of new sleep research activities in multiple fields including psychiatry, pulmonology, infectious diseases, computational science, bio-engineering, sports science, cognitive clinical psychology.

The IRC succeeded not only in improving our understanding of sleep per se but also in providing a new window to look into basic and clinical mechanisms in physiological and cognitive systems that are associated with wakefulness.

Overall, we recognize the following highlights of the IRC research consortium in its first four years of existence:

1) better understanding through experimental and human approaches of the key-role of the **thalamus** in controlling sleep-wake as well as cognitive and pain mechanisms
2) recognition of new sleep-related interventions to improve **learning** and **cognitive** performance and to better understand **conscious** experiences and **creativity**

3) improvement of our insights into the role in humans of sleep and **sleep disorders** (e.g. sleep apnea) as modulators of **mental** (e.g. depression, psychoses) and **brain** (e.g. stroke, epilepsy, coma, narcolepsy, neuro-infectious diseases, Parkinsonism) disorders and recognition of new **sleep-related biomarkers** to improve their diagnosis and treatment
4) establishment of new **computational** and **machine learning approaches** to model and analyze neural functions during sleep, wakefulness and related pathological conditions.
5) creation of new platforms (**NeuroTec**), laboratories (**Sleep Motion Lab**) and units (**Sleep House**) to promote sleep research and novel approaches (e.g. telemedicine, wearables devices) to make the management of patients with sleep and related disorders more efficient
6) launch of new educational programs: International **Postgraduate Sleep Master** (60 ECTS), **Neuroscience Bachelor** (30 ECTS) and training of over 40 young scientists (Postdocs, PhDs, MD-PhDs, Clinical PhDs, master students)
7) a total of **101 publications**, **10.6 million CHF** in research grants and one European patent application.

A2. Outlook into Extension Phase of the IRC "Decoding Sleep"

The extension of the IRC Decoding Sleep will help us solidify the basic, human, and computational research clusters of the IRC in order to guarantee a lasting and self-sustaining consortium in the international sleep research landscape. The extension has the aim to acquire important external funds and continue IRC's mission in developing a truly interdisciplinary sleep research, situated in different faculties at the University of Bern.

Concrete actions for the next two years include the following measures:

1) Integration of **new researchers** and PI's, to continuously extend the Bernese interdisciplinary sleep research network: K. Schindler (epilepsy and dementia), NeuroTec; T. Nef (biotechnology), ARTORG and NeuroTec; T. Berger (internet-based interventions, e-mental health), Psychology, Sleep House; D. Erlacher (sleep and sport), Psychology; : Brill (sleep apnea), Pulmonology, Sleep house; O. Franco, Social and Preventive Medicine, sleep house; R. Auer, Family Medicine, sleep house; Simone Duss (insomnia)/A. Vorster (sleep and sport), Sleep House, Neurology; M. Baud (epilepsy and chronobiology), Neurology; S. Saxena (sleep and neurodegeneration), ZEN and Neurology, J. van der Meer (data science), Neurology and NeuroTec;
2) Further technological developments of the platforms **NeuroTec, Sleep House** and **Sleep Motion Lab** (Institute of Psychology) to foster novel and interdisciplinary approaches in sleep research.
3) Acquisition of new **competitive funds**: two ERC applications and several new SNF proposals have been submitted and two Sinergia applications are currently in preparation. Two PI of the future IRC leadership (Antoine Adamantidis, Athina Tzovara) representing the three main clusters will prepare a new **NCCR submission**.
4) Further development of **national** and **international collaborations** (Germany, Israel, The Netherlands, China, France, Italy, Hungary, Canada, USA)
5) Remodeling of the in 2018 launched **post-graduate sleep training** (Academy of Sleep and Consciousness, https://www.asc.unibe.ch) in collaboration with the European Sleep Foundation)
6) Creation of a **pre-graduate sleep training** at the Medical Faculty, and sleep related seminars and courses provided at the Human Sciences Faculty.
7) **Special issue** of the journal Clinical and Translational Neuroscience (CTN) dedicated to the IRC Decoding Sleep

8) Launch of the new webpage "Sleep Bern" to promote communication within and with researchers of the University of Bern
9) Antoine Adamantidis and Athina Tzovara will be invited to join the IRC board of directors starting in summer 2022.

B. REPORTS FROM THE IRC GROUPS

Cluster 1: Basic Research

B1. Brain Circuits of Sensory Perception during Sleep-Wake (Antoine Adamantidis)

This project aims to investigate the thalamo-cortical circuit dynamics upon auditory stimulation across sleep states (i.e. wakefulness, NREM, and REM sleep) using single-unit activity and local field potential (LFP) activities recorded in freely-moving mice. Our hypothesis is that auditory-evoked slow waves travel across several brain areas, some of which are in the medio-dorsal thalamus that control auditory-evoked awakenings.
The three main goals of our project have now been completed. In the remaining time, we need to increase the number of animals and we want to include a new set of experiments with an imaging technique in order to confirm our main results.

Study 1. Auditory processing during sleep. Where do auditory-evoked potentials travel during sleep? We recorded and quantified the evoked-related LFP activity recorded from multiple brain areas (Au1, CMT, MG, HP) in response to 100-ms 5 kHz 80 dB tone in freely-moving mice (n=5). We found that auditory stimuli induced a similar evoked responses during wakefulness and REM sleep whereas its amplitude was higher during NREM sleep. Interestingly, the first region to be activated during NREM is the Au1, and just after 5 ms the CMT is activated, before the MG and HP. This fast response of the CMT suggests a central role of this nucleus in sensory-processing of the auditory stimuli during sleep.

Study 2. Auditory-evoked awakening from sleep. What is the thalamic contribution to auditory-evoked awakening? In order to investigate the complex mechanism of state transition across sleep-wake cycle we analyzed the averaged LFP activity in response to the tone, splitting the recording in two groups. The first group contains events in which the animals are waking up after the stimulus onset (NREMs-WAKE); the second group events in which the animals are continuing to sleep (NREMs-NREMs).
First, we wanted to investigate the role of spindle oscillations in this arousal mechanism during auditory-stimulation. Our analysis confirmed the sleep-protective role of spindles with a higher incidence of spindles when the animals do not tend to wake up, remaining in NREM sleep. In collaboration with Florence Aellen from the Athina Tzovara lab, we trained her classifier EEGNet with the electrophysiological recordings filtered in the sigma band in order to evaluate in which nuclei there was the highest discriminative activity in the two conditions (NREMs-WAKE or NREMs-NREMs). This computational approach pointed out the role of CMT nucleus in the auditory-evoked awakening. Furthermore, we analyze the slow wave influence on the auditory-evoked awakening.

In this analysis, we showed that animals significantly woke up from NREM sleep when the stimuli were delivered on the up phase of CMT slow waves, suggesting a key role for the CMT in mediating sensory-evoked arousals. Since we found that the amplitude of the auditory-evoked LFP response of the CMT was higher when the animals tend to wake up, we used an opto-genetic approach in order to modulate this auditory-evoked awakening. Opto-silencing of the CMT concomitantly to auditory stimulation significantly decreased the percentage of auditory-evoked awakening.

Study 3. Danger versus safety auditory stimuli during sleep: What is the thalamic contribution to the discriminative ability during sleep? To test whether the information associated with auditory cues – i.e., danger (conditional stimuli, CS+) versus safety (CS-) – was differentially processed during sleep, we performed an auditory cued fear conditioning followed by re-exposure to CS+ and CS- cues during subsequent sleep with CMT opto-silencing (n=19). Our results showed an increase in the percentage of awakening from the CS+ after the conditioning, suggesting that the discriminative ability persisted during NREM, but not during REM sleep. The CMT opto-silencing compromise this stimuli discrimination, decreasing the percentage of awakening from the cued-stimuli. Taken together, our results showed that CMT neurons are central to the processing of environmental auditory cues associated with danger.

B2. The Role of the Thalamus in Sleep, Sensory Processing and Cognition (Carolina Gutierrez-Herrera)

The role of the thalamus in sleep-wake regulation, based on conflicting experimental and human observations, remains controversial. This project aims to investigate the role of specific thalamic nuclei in sleep, sensory processing and cognitive processes in mice with the hypothesis of distinct contributions of the different thalamic areas.

To optimize current photothrombotic stroke models and to allow the study of subcortical strokes in awake behaving mice, we targeted different regions irrigated by the paramedian or tuberothalamic arteries via targeting to three discrete brain areas: 1) the intralaminar (IL) functional thalamic class (CM, Pf, CL), 2) the reticular thalamic nucleus (TRN), or 3) the anterior thalamus (AD, AM, AV). Quantification of the volume of ischemic infarcts across different stroke locations were consistent in size and restricted to the targeted nucleus. We further characterized changes in connectivity to their postsynaptic targets using an anterograde viral vector stereotactically injected in targeted areas. To track circuit-specific synaptic changes, relevant for sleep modulation and cognition, we quantified thalamic synaptic contacts onto cortical interneurons. Quantification of axonal contacts onto immunoreactivity PV+ interneurons revealed a dramatic reduction in the number of central thalamic puncta in Opto-Stroke as compared to sham animals. This model has two unique characteristics: 1) targeting subcortical brain nuclei with precision and reproducibility and 2) stroke induction without the use of anesthetics that enable the tracking of stroke and brain dynamics development of the stroke.

Study 1. Characterization of sleep macro and microarchitecture in thalamic OPTO-stroke. We found that central thalamic Opto-stroke animals showed an increased number of switches from wakefulness to NREM and NREM to wakefulness. In addition, the increase of the delta frequency band and decrease in gamma power was long lasting (over 20 days). Together, this suggests an increase in wake instability. Over the semi-chronic phase (day 2-20) wake to NREM transitions remained higher in number compared to the sham animals. Interestingly, we found an increase in episodes and duration of a transitional state between wake and NREM characterized by intrusion of slow waves, a high power in the band of 10-13 Hz, analogue to NREM stage 1 in humans which is also increased in paramedian thalamic stroke patients. Further, central median Opto-stroke resulted in frontal- parietal dissociation of the sigma band (11-16 Hz) with a decreased in the frontal EEG power and spindle rate, which spontaneously recovered by the third week after stroke. First results of this study were recently published (Lenzi et al., bioRxiv 2021). Figure 1 provides an overview of the experimental steps.

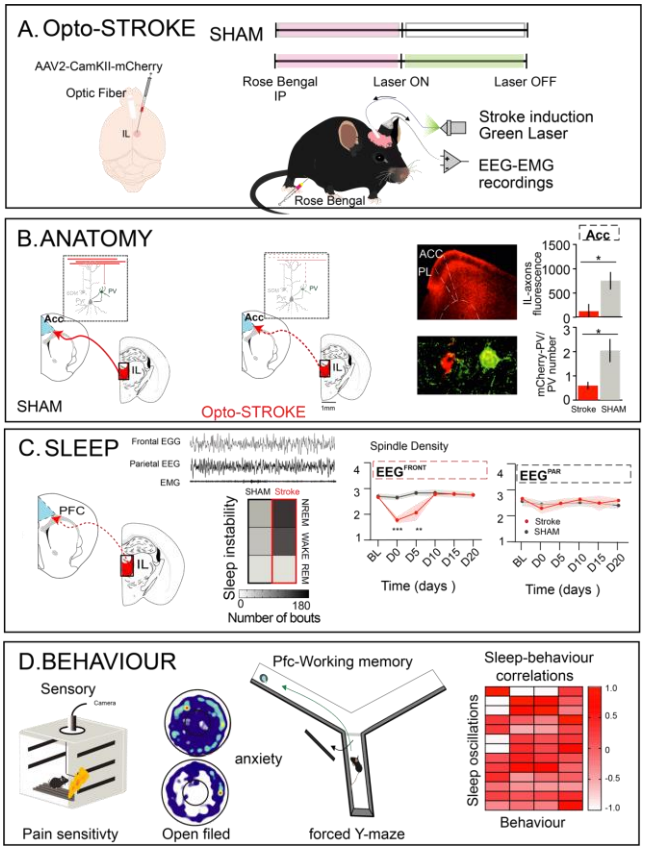


Figure 1. A. Schematic description of optical induction of mini photothrombotic strokes (OPTO-Stroke). **B.** Histological characterization of intralaminar thalamic nuclei (IL) OPTO-stroke. IL stroke induces degeneration of axonal contacts particularly to parvalbumin+ interneurons in the anterior cingulate cortex (ACC). **C.** IL OPTO-Stroke results in increases in arousal stability and reduces sleep efficiency compared to SHAM control animals. Microstructure of sleep is topographically affected in specific spindle rate and the gamma power. **D.** characterization of sensory (pain) processing and working memory were negatively correlated with gamma power at the day of stroke and with the spindle

Study 2. Correlation between sensory and cognitive processing to sleep parameters. To investigate changes at the behavioral level, animals were tested for anxiety, pain and working memory, which are typically found in paramedian stoke patients. We found that central median Opto-stroke animals show and increased pain sensitivity and show a reduction of correct responses in a working memory test when compared to sham animals. However, no significant changes were found in motor, exploration and anxiety between experimental groups, indicating the specificity of the lesions. We then correlated the scores in pain and memory with specific features of macro and micro sleep architecture. We found that the gamma power during the 24hr after stroke induction and the spindle rate during the second week after stroke correlated with performance during these tasks. Lastly, we found anatomical changes in the number of thalamic synapses onto PV+ interneurons in the ACC, which has been associated to regulate pain responses and working memory.

B3. Hypothalamus and sleep: REM Sleep Propensity, Cataplexy and Thermoregulation in a rodent model of narcolepsy (Markus Schmidt)

Narcolepsy is characterized by increased REM sleep propensity and cataplexy. It is caused by the selective loss or dysfunction of hypocretin (Hcrt) neurons within the lateral hypothalamus (LH). Our project aims at a better understanding of the mechanisms underlying REM sleep propensity and cataplexy. We have recently shown that wild type (WT) mice increase REM sleep expression when exposed to thermoneutral ambient temperature (Ta) warming during the light (inactive) phase. Accordingly, our hypothesis is that the loss of Hcrt may lead to exaggerated responses with respect to increased REM sleep and cataplexy during Ta warming. This project was started in the summer of 2019, much later than the other IRC groups. As a result, we are only approximately 50% complete. The PhD student, Bianca Viberti, will complete the project in the summer of 2023.

To test our hypothesis, Hcrt-KO mice were implanted for chronic sleep recordings and housed in a temperature-controlled cabinet. Sleep-wake expression and both spontaneous cataplexy and food-elicited cataplexy were evaluated at constant Ta and during a Ta manipulation protocol. Here we show several unexpected findings. First, Hcrt-KO mice show opposite circadian patterns with respect to REM sleep responsiveness to thermoneutral Ta warming compared to WT mice. As previous demonstrated, WT mice increased REM sleep when Ta warming is presented during the inactive (light) phase, whereas Hcrt-KO showed a significant decrease in REM sleep expression. In contrast, Hcrt-KO mice increased REM sleep expression upon exposure to Ta warming when presented during the active (dark) phase, a circadian time when WT mice showed no significant changes in REM sleep as a function of Ta. Second, we found that REM sleep and cataplexy can be dissociated through Ta manipulation. Specifically, although Ta warming significantly increased REM sleep expression in Hcrt-KO mice during the active phase, cataplexy bout number and total cataplexy duration significantly decreased. In contrast, cataplexy expression was favored during Ta cooling when REM sleep expression significantly decreased. Finally, video actigraphy and sleep-wake recordings in Hcrt-KO mice demonstrated that Ta manipulation did not significantly alter waking motor activity patterns or waking or NREM sleep durations. These data suggest that neural circuits gating REM sleep and cataplexy expression can be dissociated with Ta manipulation.
Our current work includes calcium imaging of MCH neurons using fiber photometry in both MCH-cre and Hcrt-KO/MCH-cre mice. This methodology will allow us to understand dynamic activity of MCH neurons in both baseline and Ta warming conditions, as well as to compare this activity with narcoleptic mice during REM sleep and cataplexy. Finally, we have also employed optogenetic manipulation of MCH neurons in narcoleptic mice to test the hypothesis that the MCH system plays an important role gating of cataplexy expression.

B4. Brain Circuits of Sensory Perception during Sleep (Thomas Nevian)

Sleep and pain are frequently associated in humans. A better understanding of this relationship may offer options for new, sleep-dependent improvement of chronic pain. This project is based on the hypothesis of a bidirectional link between sleep and pain mechanisms, aims to characterize 1) the processing of painful and non-painful mechanical stimuli during sleep and wake, 2) the effect of chronic pain on sleep and sensory processing during wakefulness and sleep in thalamo-cortical and hippocampal loops in mice. The IRC project is still ongoing. We expect to finish it completely at the end of 2022.

Study 1. Understanding of the processing of painful and non-painful mechanical stimuli during sleep and wake. The first project is finished and a manuscript in preparation. Here we investigated the processing of noxious and non-noxious stimuli during sleep and wake in the somatosensory and anterior cingulate cortex and their corresponding thalamic nuclei. Both brain areas are key players

in cortical pain processing. The major finding was that the sensory stimuli resulted in activation of both cortical and thalamic areas during non-REM sleep. Thus, cortical sensory processing also occurs during sleep. The novel observations we made in the last year were that the behavioral reaction depended strongly on the brain state before the stimulation. For example, if delta-power is high in the anterior cingulate cortex before stimulation, the animals do not wake up from non-noxious stimulation. However, this protection from waking up was not observed with noxious stimuli. Furthermore, we found that the behavior of the animal during wake was mainly determined by processing in the somatosensory cortex, while the reaction in sleep was controlled by the state of the anterior cingulate cortex. Thus, cortical oscillations during sleep determine pain processing and arousal from sleep is differentially dependent on the brain region.

Study 2. The effect of chronic pain on sleep and on sensory processing during sleep. In the second project we were investigating the impact of chronic pain on cortical oscillations. We found that the resting state power spectrum in quiet awake animals was impaired in chronic pain in the anterior cingulate cortex. The maximal power was shifted to lower frequencies and the peak power was larger than in sham controls, suggesting increased synchrony in the chronic pain state. We have investigated the cellular origins of this change in cortical oscillations and have found that the downregulation of the hyperpolarization activated and cyclic nucleotide dependent ion channel (HCN channel) in pyramidal neurons and a loss in cortical inhibition might explain the phenotype. Pharmacological enhancement of HCN channel function recovered the resting state dominant frequency, but not the increase in power. This suggests that HCN channels might determine the dominant frequency, but that inhibition is important for the synchronization of the neuronal network. We are currently finalizing the manuscript of this completed project. The manuscript is already available as preprint. In order to corroborate the experimental findings, we developed in the last year a theoretical network model with the theoretician Dr. Katharina Wilmes (co-supervised by Walter Senn). The simplified model was oscillating and modification of HCN channel density and inhibition qualitatively reproduced our experimental findings.

Cluster 2: Human Research

B5. Sleep-Wake Disturbances Following Tick-borne Encephalitis (Stephen Leib)

Tick-borne encephalitis (TBE) is a common non-bacterial meningo-encephalitis. Longterm sequelae of TBE include sleep-wake disturbances (SWD), which are poorly characterized and understood. Our project aims to investigate the frequency, characteristics and underlying mechanisms of SWD in TBE using a combined human and experimental approach. The 3 main goals of our project have now been completed.

Study 1. Prevalence, clinical characteristics of sleep-wake disturbances after tick-borne encephalitis (TBE). A literature research was performed in accordance with PRISMA guidelines. The quality of the papers was assessed using a standardized quality assessment. The analysis of sleep wake circadian disturbances (SWCD) was categorized into four different time intervals and two age groups. We identified 15 studies, five including children and 10 including adults. In children, fatigue was most frequently observed with a prevalence of 74%, followed by somnolence/sleepiness, restlessness, and sleep-wake inversion. In adults, tiredness/fatigue was the most reported sequela with a prevalence of 27% followed by extensive daytime sleepiness/somnolence, and insomnia. Two

studies showed impaired social outcome in patients after TBE infections. In conclusion, we found that SWCD after TBE in children and adults is a newly recognized sequela.

Study 2. Retrospective analysis in clinical sample. 258 patients suffering from meningitis, meningoencephalitis or encephalitis from the Berne area were considered. Non-bacterial meningoencephalitis was most likely caused by tick-borne encephalitis virus (TBEV). At a follow-up period of 16 months, one third of the meningoencephalitis patients reported new onset of fatigue or extensive daytime sleepiness (EDS) or both (Dietmann et al., BMC Neurology 2021).

Study 3. Experimental in vivo study in juvenile rats using Langat Virus infection (LGTV). To the best of our knowledge, this was the first study ever assessing the consequences of neuro-infection caused by LGTV infection in wild-type rats over such an extensive time, combining inflammatory parameters, behavior results and the assessment of sleep-wake behavior. The major novelty of this study was the identification and characterization of the sleep-wake disorders after LGTV infection. We observed that the infected animals spent significant more time awake and significantly less time in REM sleep in the light period, when they are usually sleeping. In the dark period (active period), the infected animals spent significantly more time awake and therefore significantly less time in NREM and REM sleep than the healthy animals. The results from this study help to provide a real milestone in better understanding the long-term effects of TBE.

B6. Sleep Subtypes in Adolescent Depression: Sleep Physiology and Treatment (Leila Tarokh)

Our project aims to assess sleep changes in adolescents with depression as potential new markers for new diagnostic and treatment approaches. The main hypothesis is that sleep efficiency and slow wave sleep may be altered and serve as predictors of outcome in adolescent depression.

Study 1. Slow-wave activity in adolescents with major depressive disorder (MDD). We have now completed enrollment in our study and recruited 35 participants with major depressive disorder and 35 age and sex matched controls. One of the challenges we encountered during enrollment was the recruitment of a medication free sample of depressed adolescents with moderate to severe depression. The absence of medication in our sample affords us the ability to understand the neurobiology of depression and makes our studies one of the largest in a medication free sample of depressed adolescents. We find significantly diminished slow wave activity, a marker for deep sleep, in adolescents with major depressive disorder (MDD) over widespread cortical regions, with large effect sizes. Our findings suggest impairments in the sleep homeostatic system in adolescents with depression.

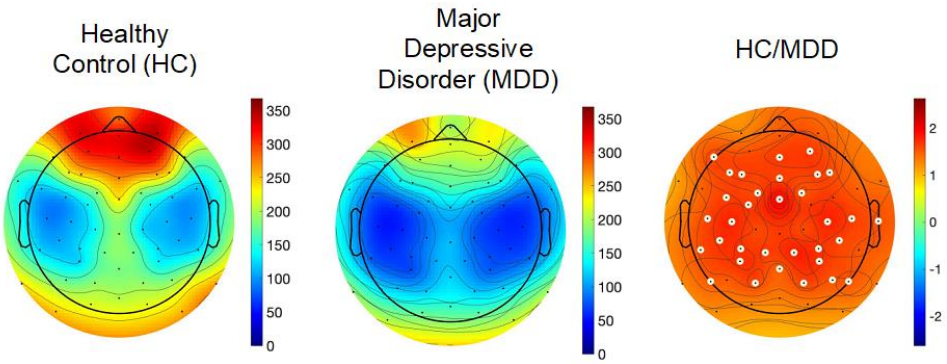


Figure 2. Topographic distribution of slow wave activity (SWA; power from 0.6 to 4.6 Hz) for healthy control versus participants with depression. Participants with depression showed on average a 1.5 times decline in power across brain regions as shown in the third panel (significant electrodes shown with a white dot).

Study 2. Longitudinal associations between depression and sleep. We follow participants longitudinally for one year collecting data about sleep and mental health monthly via online questionnaires. With this design we were able to distinguish the temporal association between sleep and mental health, finding that more depressive symptoms resulted in shorter total sleep time and lower sleep quality. On the other hand, we found a reciprocal relationship between sleep efficiency and sleep latency suggesting that by improving sleep, we can also improve depressive symptoms.

B7. Creativity and Sleep (Rene Müri)

Few mainly anecdotal reports suggest a role of sleep in creativity. This project is based on the hypothesis of a direct link between sleep and creativity. The association between the performance in verbal and figural divergent (DT) and convergent thinking (CT) and sleep macro- as well as micro-architecture is investigated. Completion of this project is scheduled for the end of February 2022.

Study 1. Creativity and sleep macro- and microarchitecture. 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-architecture level, an increase in N1 sleep was associated with increased fluency in verbal DT (rs(40)=.331, p=.037). While an increase in N2 sleep was positively correlated to verbal creative problem solving in CT (rs(40)=.341, p=.031), an increase in N3 sleep was associated with higher scores in figural DT (rs(40)=.320, p=.044). Moreover, an increase in REM sleep was associated with a better performance in figural CT (rs(40)=.-352, p=.026). On a micro-architecture level, higher originality in figural DT was correlated with lower slow wave power (rs(40)=-.434, p=.005). Figure 3 summarizes the main findings on the macro- (panel A.) and micro-architecture level (panel B.). 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.

Study 2. Short naps and performance in creativity tasks. This experiment is ongoing, and will be completed by the beginning of 2022.

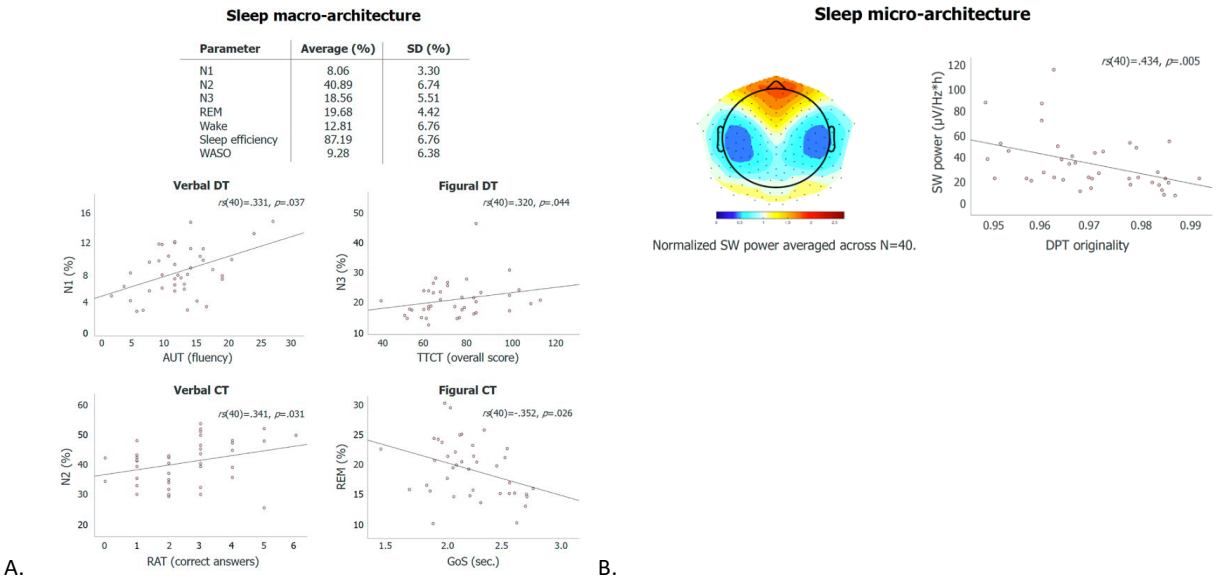


Figure 3. A. Graphical summary of the main results on the macro-architecture level. **B.** Graphical summary of the main results on the micro-architecture level. AUT – alternative uses task, TTCT – Torrance test of creative thinking, RAT – remote associates task, GoS – game of shadows, DPT – divergent pareidolias task.

B8. Learning during Sleep Enhances Wake-Learning (Katharina Henke)

We investigate the hypothesis of a direct role of sleep on learning, and we aim to examine whether 1) the vocabulary of a new language can be acquired during slow-wave sleep and 2) this form of declarative sleep-learning enhances subsequent declarative wake-learning, and characterize the underlying neural networks, like hippocampus and neocortical language areas, with fMRI, and the neural events, like sharp-wave ripples and slow-oscillation up-states, with EEG.

We published evidence of successful vocabulary learning during up-states of sleep slow-oscillations (Züst et al, Current Biology, 2019) and a review article on sleep-learning (Ruch & Henke, Trends in Cognitive Science, 2020) as well as a report on how and why sleep-learning impairs the subsequent wake-learning of the same information (Ruch, Züst & Henke, Neurobiology of Learning and Memory, 2021). In addition, we have developed and submitted for publication an article on the technical development of a closed-loop algorithm for sleep research (Ruch, Schmidig, Knüsel & Henke, Journal of Neuroscience Methods, submitted). We have implemented this novel closed-loop stimulation algorithm, which allows targeting auditory stimulation to up- or down-states of local slow-oscillations, in the main PhD work of Flavio Schmidig. He has used this newly developed algorithm to find out how the state of slow-oscillations determines whether new vocabulary can be learned during deep sleep. Flavio's statistical evaluation of the behavioral and EEG data collected in this project took over a year but led to interesting and reliable results: the findings indicate that vocabulary is learned and retained for > 36 hours if played during an ongoing down-state and then processed during the following up-state of slow-oscillations. The paper on this discovery is almost ready for submission (Schmidig et al., Neuron, in preparation). Finally, we have accumulated evidence that memory consolidation during slow-wave sleep not only benefits consciously but also unconsciously (based on subliminal movies) formed memories (Pacozzi et al., Nature Human Behavior, in preparation). This is evidence that deep sleep supports not only the consolidation of consciously acquired information but also - and even more so – the consolidation of unconsciously acquired information.

B9a. Thalamus and sleep: Insights from patients with stroke (Claudio Bassetti)

The thalamus is suggested to play a key role in sleep-wake regulation and cognitive functions. To increase our understanding on the role of specific thalamic structures on sleep, wakefulness and cognition two human studies on thalamic stroke patients were performed to complement the experimental approaches presented in B2 (Gutierrez-Herrera).

Study 1. Thalamic stroke and high-density EEG. From a previously series (SNF CRSII3_160803), patients with thalamic (n = 15) and extrathalamic (n = 11) stroke were selected for a detailed analysis. Sleep was studied by polysomnography (PSG) and high-density EEG in patients. The extension of the lesion was quantified by MRI. In the evening before and morning after PSG, subjective sleepiness (Epworth Sleepiness Scale, ESS) and tests of language, neglect, verbal memory and visual memory were performed.

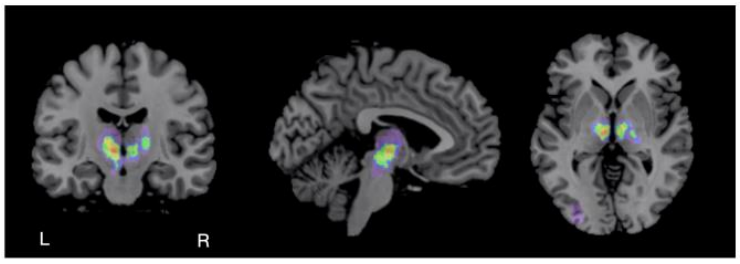


Figure 4: Magnetic resonance diffusion-weighted images of thalamic stroke patients (overlap).

Patients with intralaminar and mediodorsal thalamic nuclei stroke, had higher ESS and proportion of NREM1, longer wake episodes and more NREM-wake transitions. In a first analysis, overnight slow wave slope changes were found to be reduced in a large cluster of electrodes in thalamic compared to extra-thalamic stroke patients. This reduction was related to increased ESS. Both a reduction in attention during wakefulness and an impairment in synaptic renormalization during sleep may account for the reduced overnight slope changes found in thalamic stroke patients (Jaramillo, Ann Neurol 2021).

In a second, still ongoing analysis the sigma power was the lowest when the thalami were bilaterally (medially) lesioned (Linear mixed-effects models, LMM, E=-1.3655, p<0.001). Individual spindles detected frontally from patients with unilateral medial left or right or with bi-thalamic lesions were of significant lower power than age-/gender- matched controls or than the spindles from patients with a lateral thalamic lesion (LMM, p<0.001). Additionally, the power reduction in frontal channels was topographically lateralized (ipsilateral), in case of unilateral medial lesions. The frontal reduction was generalized, in case of bi-thalamic lesions. The individual spindles from posterior emergence were of lower power in all thalamic lesions, without distinct topographical distribution.

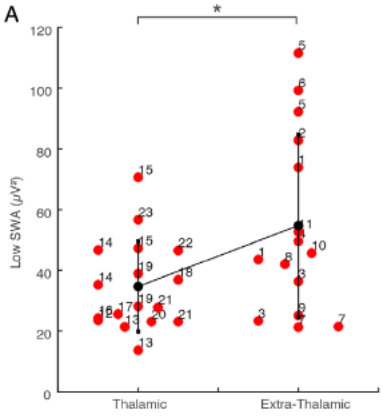


Figure 5: Comparison of all night low slow wave activity (SWA) and power in other frequency bands between thalamic an extrathalamic stroke patients. Red dots show global SWA (average across all electrodes) for each night recording. The horizontal bar and asterisk denote a significant difference between thalamic and extrathalamic patients (p = 0.022).

Study 2. Specific impact of thalamic lesions on sleep EEG, vigilance and cognition. In a prospective approach patients with an acute and isolated thalamic or basal ganglia stroke were considered. Overall, 1800 patients were screened, of whom 59 with a thalamic and 64 with a basal ganglia stroke. A total of 16 patients (15 with a thalamic lesion, 5 females, 63± 9 years) were assessed by (PSG) and high-density EEG, detailed neuroimaging and cognitive tests (see above) were performed. In a still ongoing analysis, patients with anteromedial thalamic stroke had shorter duration of NREM3 sleep p=0.011) and a higher ESS score (p=0.037) than patients with lateral thalamic stroke. ESS score showed a negative correlation with the duration of NREM3 sleep (Spearman correlation: r=-0.90, p<0.01). A detailed analysis of these data is planned for the first half of 2022.

Overall, these results suggest that thalamic stroke has different effects on daytime vigilance, cognition and nocturnal sleep EEG (e.g. slow wave slope, sigma power) which differ according to the involvement of specific thalamic nuclei and are more important than in patients with extra-thalamic strokes with a comparable stroke severity. An assessment of the correlations between sleep EEG, vigilance and cognitive changes over time is planned.

B9b. Hypothalamus and sleep: The Swiss Primary Hypersomnolence and Narcolepsy Cohort Study-SPHYNCS (Claudio Bassetti, Markus Schmidt)

Narcolepsy with cataplexy and hypocretin deficiency (NT1) is a disorder with well-established markers and a suspected autoimmune etiology. Conversely, the narcoleptic borderland (NBL) including narcolepsy type 2 lack well-defined markers and remain controversial in terms of etiology, diagnosis, and treatment. SPHYNCS is a multicenter cohort study, which has the primary aim to find new markers for the NBL. Clinical (e.g. questionnaires) and neurophysiological data (from

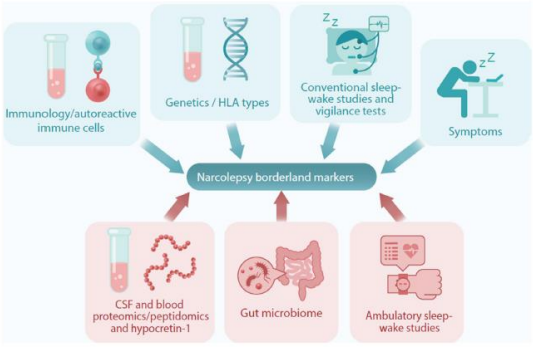


Figure 6: Multimodal study design with the aim to identify novel markers for the narcoleptic borderland (NBL). Established methods (i.e. genetic, immunological and neurophysiological) are combined with new technologies (highlighted with red frames: i.e. microbiome, peptidome, longterm activity tracking with Fitbit) in order to validate well known and identify novel disease biomarkers.

polysomnography, MSLT, MWT, actigraphy, Fitbit) will be collected at baseline and during a follow-up of 3 years. Additional biomarkers will searched for in blood, cerebrospinal fluid, and stool. Patients with NT1 and NBL as well as healthy subjects and patients with EDS due to severe sleep disordered breathing will be included. Analyses will include spectrometric hypocretin measurements (in collaboration with C. Largiader, University of Bern), peptidomic (T. Mann, University of Munich, Germany), immunological (F. Sallusto, ETH Zurich), genetic (M. Tafti, EPFL, Lausanne) and microbiotia (A. MacPherson, University of Bern) studies. The marker profiles from the different data sources will be analyzed and integrated using appropriate approaches including machine learning based algorithms (A. Tzovara, University of Bern).

This project, which was initially funded by the SNF, and then included in the IRC in 2019, and officially started in Spring 2020. The protocol of the study was published (Dietmann et al, J Sleep Res 2022). Two new clinical PhD students were recruited (E. Wenz. L. Fregolente-Gomes) and their support secured by grants independent from the IRC. To date, seven Swiss sleep centers, belonging to the Swiss Narcolepsy Network (SNaNe), joined the study and prospectively enrolled 70 patients. The involvement of international partners (Bologna, Italy; Witten-Herdecke, Germany) is planned for the beginning of 2022.

B10. Closed-Loop Manipulation of Sleep Slow Wave Activity to Treat Depression (Christoph Nissen)

Our project, which is based on the hypothesis that sleep-related approaches may improve depression, aims to test the primary hypothesis that slow wave sleep (SWS) suppression may have an antidepressive effect.

The construction of two novel sleep research labs at the psychiatric hospitals (UPD) campus was completed in spring 2020. Both labs provide the opportunity of state of the art hd-EEG recordings, complemented by neurophysiology opportunities, including TMS and tDCS. These developments have been supported by UPD funding.

Within the IRC project, a fully automated approach to suppress slow wave sleep was developed and implemented. The SWS detection and closed-loop SWS suppression through auditory stimulation is shown in Fig. 7. During the intervention night with SWS suppression, auditory stimulation is applied during SWS using in-ear headphones. The auditory stimulation involves bursts of pink noise with a volume increasing up to 106 dB, until SWS is no longer detected by the algorithm (Fig. 7 C-D). A maximum of 120 min of stimulation at maximum volume (106 dB) can be applied throughout the night. This is in accordance with noise protection safety regulations of the WHO. The SWS detection algorithm was developed in the lab of Katharina Henke, University of Bern, and adapted by our lab to allow for robust all night SWS detection, across different age and patient groups. The auditory stimulation algorithm was developed with the support of the research group of Walter Senn. In a longer line of research in healthy humans, we demonstrate successful suppression of SWS and SWA

across the night (Fig. 8). The final algorithm includes randomized auditory stimulation (pink noise, 50-500 ms, 1-4 s interim interval, 40-106 dB random walk) and has been validated in n=13 participants (adaptation, sham and stim night). Other protocols showing less efficacy with regard to SWS suppression (such as constant tones or slow wave downstate application) have been tested in n=50 participants, resulting in about 200 overnight recordings in the sleep laboratory. These developments indicate that the suppression of SWS through auditory stimulation is more difficult than initially anticipated.

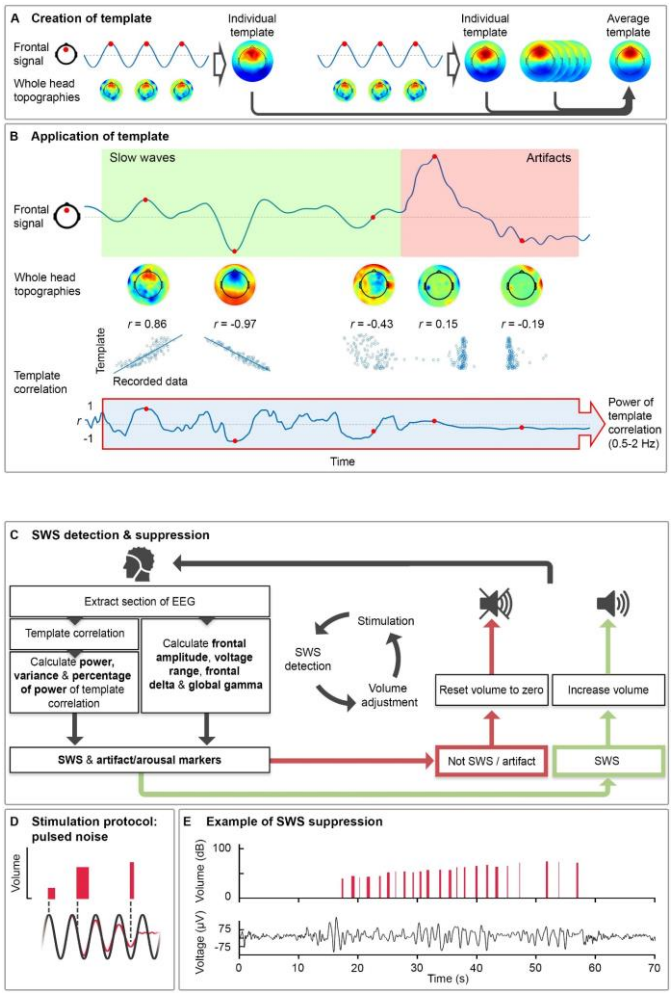


Figure 7. Creation and application of a spatial template of frontal slow waves, for SWS detection and closed-loop SWS suppression through auditory stimulation. **A.** Creation of template. Fronto-central slow waves are detected. The whole head potentials at the time-point of a frontal slow wave peak are recorded, averaged across all instances, and normalized to create a spatial template of frontal slow wave peaks per individual. Finally, an average template is created across individuals. **B.** Application of template. Whole head potentials are first correlated with the template. The correlation is positive upon frontal slow wave peaks, negative upon troughs, while the correlation decreases between peaks and troughs or for artifacts. The power of the distinctive ~ 1 Hz rhythmic fluctuation of the correlation over time is used as a marker for SWS, with the advantages of being insensitive to amplitude differences and robust against artifacts. **C.** SWS detection and closed-loop SWS suppression through auditory stimulation. The template correlation is calculated over a moving window of EEG signal. The power, variance of power and percentage of power are used together with global gamma power to detect SWS. Frontal amplitude, voltage range and delta power together with global gamma power are used as artifact and arousal markers for quick suppression of the stimulation. **D.** Illustration of the pulsed noise stimulation protocol. Upon detection of SWS, bursts of pink noise are applied with a randomized duration and inter-onset interval. A random walk (Ornstein-Uhlenbeck process) is superimposed on a linear increase of volume, to add unpredictability in volume. **E.** Illustration of SWS suppression through pulsed noise of increasing volume.

Effects of the final version of the algorithm were investigated in a randomized controlled within-subject repeated measure pilot study in healthy humans (n=13) across three sleep laboratory nights (adaptation, stimulation, sham; counterbalanced design). We observed a significant suppression of SWS in the stimulation compared to the sham condition (Fig.2A). Lighter NREM sleep (N2) was increased (not visualized). No other significant changes in sleep continuity (including sleep duration) or architecture (including parameters of REM sleep) were observed (not visualized). EEG slow wave activity (SWA) averaged across NREM sleep was reduced by about 30% in the stimulation as compared to the sham condition (Fig. 8B), without changes in other frequency bands (not visualized).

These data provide, to our knowledge, the first evidence for the feasibility and efficacy of fully automated SWS suppression through auditory closed-loop stimulation in humans. The further IRC

project is designed to translate this technology, for the first time, to patients with MDD to test the hypothesis of antidepressant effects of automated SWS suppression.

These developments are reflected in a current European patent application with the support of Unitectra (University of Bern): A sleep-based detection and intervention system (1) for treatment of major depressive disorder (Attorney Ref.: P6320EP00). Parties involved in this application include the research group of the PI of the current project (C. Nissen), Simon Ruch of the research group of Prof. Katharina Henke and Prof. Walter Senn. This patent application directly addresses the aim of the IRC to promote interdisciplinary and translational sleep research at the University of Bern.

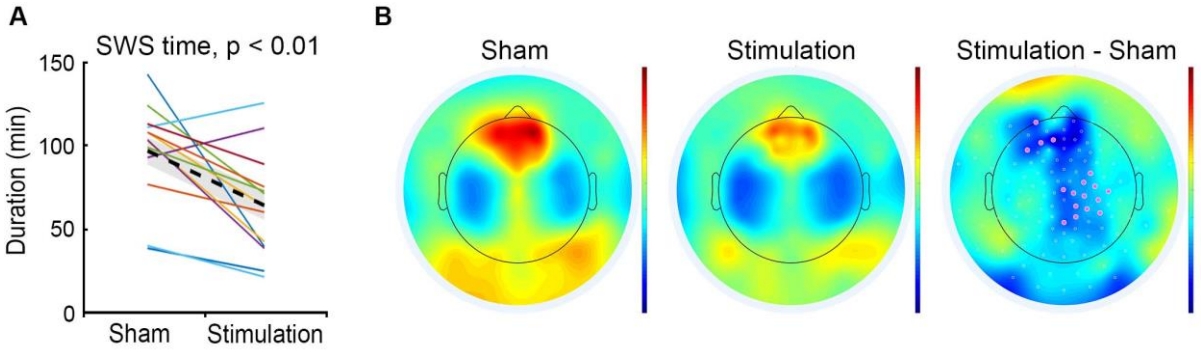


Figure 8. Proof-of-concept of fully automated slow wave sleep suppression in healthy participants (n=13) using a counterbalanced within subject design comparing auditory stimulation during slow wave sleep to sham. **A.** Suppression of slow wave sleep (SWS). Individual participants are shown as solid colored lines, while the average is shown as a dashed black line. **B.** Suppression of EEG slow wave activity across NREM sleep upon stimulation compared to sham. Colored electrodes (far right topo plot) indicate significant differences.

B11. Reality-Monitoring in Sleep, Psychosis, and Virtual Reality (Fred Mast and Thomas König)

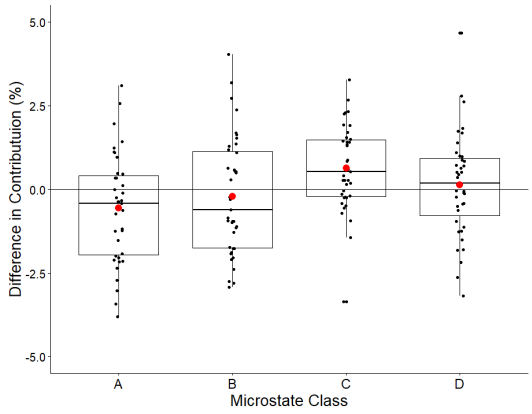


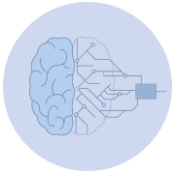
Figure 9: Mean difference in contribution of microstates between the bizarre and realistic conditions. Boxes represent the 25–75 percentile of the distribution; whiskers represent the non-outlier range. Horizontal bars within the boxes indicate median values; red dots indicate mean values; black dots represent individual values of participants.

Study 1: Reality experience using highly immersive virtual reality and EEG. The overall aim of the project was to test the hypothesis that there would be common changes in so-called EEG microstates related to the subject's experience of unusual and bizarre mental representations as something real. For this purpose, PhD student Simone Denzer successfully conducted an experiment that simulated dream-like bizarre experiences in a VR environment. She tested about 40 subjects who explored a newly designed bizarre VR environment and a neutral control environment while their EEG was recorded. The results show that the combined VR+EEG setup was able to induce experiences of bizarreness and unrealness, and that these experiences correlated with the natural variance in the presence of weak psychosis-like experiences. Also, one EEG microstate class (class C) was systematically altered in the dream-like environment (see Figure 9). Moreover, the dream-like environment reduced the subject's response to violations of their semantic expectancies in a semantic association task, as measured using EEG evoked potentials. The paper on the experimental setup and behavioral data is currently

under revision (new version with minor revisions submitted, and we expect acceptance), the paper containing the EEG microstate results is nearly ready for submission, and the paper on reduced evoked potentials in response to semantic violations is in preparation.

Study 2: EEG recording and experience sampling of healthy subject during wakefulness, sleep onset and sleep. PhD student Sarah Diezig recorded more than 40 subjects in the process of falling asleep, where as part of hypnagogic states, subjects increasingly report experiencing mental representations as real, and systematically collected spontaneous reports of ongoing mentation while recording EEG. Interestingly, the same microstate class C that accounted for bizarreness in Simone Denzer's findings was also increased when subjects reported more dream-like experiences. Within the scope of a current master's thesis, the response to violations of semantic expectancy was also found to be decreased when subjects were closer to sleep. Sarah Diezig is currently preparing these findings for publication but is somewhat behind schedule due to a prolonged period of illness.
Finally, in a collaboration with the department of child and youth psychiatry, we have also found the same pattern of EEG microstate abnormalities in a large sample of young subjects at risk for psychosis. The project's overall aim, which was to identify an overarching signature of reality monitoring that is consistently disengaged in sleep, but also in other altered states of mind, has therefore been achieved. This is an important step forward because it links phenomena related to sleep onset and dreams to psychiatrically relevant phenomena. Thus, sleep research can have a huge impact to a better understanding of phenomena in seemingly remote clinical areas like psychosis and schizophrenia.

Cluster 3: Computational Research



B12. Computational techniques to study sleep and loss of consciousness (Athina Tzovara)

Our project aim is to develop novel computational and machine learning techniques for investigating neural functions that take place during sleep or pathological loss of consciousness. We hypothesize that machine learning techniques will advance our understanding of sleep electrophysiology, and in particular, of how the sleeping brain processes information from the environment. Moreover, we hypothesize that computational techniques will enable the introduction of novel biomarkers for assisting clinical decision making for (a) predicting outcome from coma and (b) improving diagnosis of sleep disorders. We are testing these hypotheses in the following studies from our group, and in collaboration with other groups of the IRC.

Study 1. Deep learning for EEG signals. Although deep neural networks have an enormous potential to detect patterns of information from large datasets, their use for analyzing electrophysiological data remains limited. In our studies, we first aimed at developing and validating novel deep learning pipelines to classify EEG data, emphasizing interpretability (Aellen et al., 2021). We have then applied deep learning pipelines on intracranial EEG data recorded in mice within the IRC, with the goal of classifying sleep stage transitions (collaboration with A. Adamantidis). Moreover, we have used deep learning to predict outcome from coma based on EEG responses to auditory stimuli (manuscript in preparation, collaboration with CHUV, Lausanne).

Study 2. Predicting outcome from coma based on EEG responses to sounds. We published a study on coma patients, where we examine the diagnostic value of theoretical indexes of consciousness (neural integration and differentiation) in predicting outcome from post-anoxic coma. We show that the phase locking of EEG responses to sounds is predictive of the patients' chances of survival at three months. By contrast, the complexity of EEG responses and 1/f spectral exponent are indicative of the presence of conscious processing (Figure 1). This study was published in 2021 (Alnes et al., 2021, press release: http://www.inselgruppe.ch/de/aktuell/details/news/komapatienten-guenstige-prognose-bei-gleichtakt-der-hirnzellen/).

Study 3. Electrophysiological correlates of auditory processing in sleep and wake. In an ongoing intracranial EEG study in patients with epilepsy, we are investigating processing of auditory stimuli during sleep and wakefulness (S. Alnes). The paradigm was adapted from a paradigm originally developed by A. Adamantidis, in order to study parallels in auditory processing during sleep between humans and mice. Patient recordings for this study are ongoing and expected to finish in 2022-2023, depending on patient availability and the evolution of Covid. The study is in collaboration with Prof. K. Schindler, Dr. Maxime Baud, and Prof. Lukas Imbach (University of Zurich). Moreover, we have an ongoing scalp EEG study investigating learning and sensory predictions in REM and NREM sleep. Recordings for this study were performed at NeuroTec and were completed in 2021. Data analysis is ongoing.

Study 4. Analysis of data from Insel sleep database and SPHYNCS: We are analyzing clinical variables with unsupervised learning techniques, in order to improve phenotyping of patients with sleep disorders (F. Aellen, in collaboration with Prof. Bassetti and Dr. Julia van der Meer). The future plan for 2022 is to use deep learning on raw PSG signals, to classify sleep disorders and assist in diagnosis.

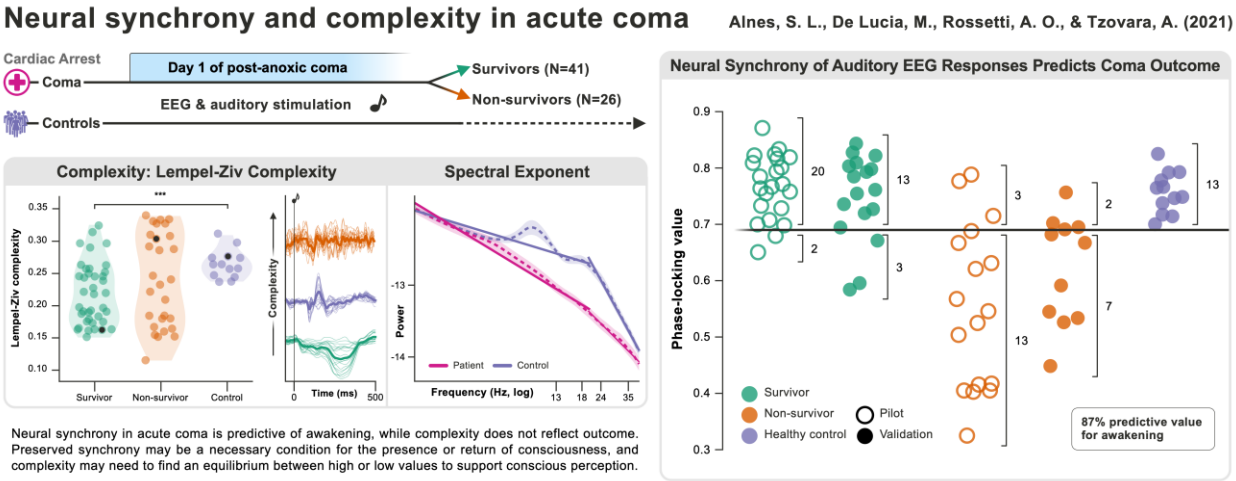


Figure 10: Neural synchrony and complexity of EEG responses to auditory stimuli in acute coma. Neural synchrony (right panel) is predictive of coma outcome, with survivors having higher synchrony than non survivors. Complexity of EEG responses (left panel) may instead need to find an equilibrium between high or low values to support conscious perception. Figure from Alnes et al., 2021.

B13. Machine Learning for iEEG and Closed-Loop Systems (Paolo Favaro)

The main objective of this project is to develop a closed-loop system based on iEEG: The system should measure, analyze, and predict iEEG and use this information to generate stimuli that can change the brain state (e.g., to avoid the onset of a seizure).

Study 1. Technical Development. We explored the option of transforming iEEG signal into a sequence of discrete tokens, which should simplify the task of classifying iEEG (e.g. for sleep scoring), making future predictions and thus designing closed-loop systems. Our key findings here are that tokenization can be achieved (statistically significant at ~85% accuracy with 100 tokens) and it can also successfully predict future tokens. However, there are several limitations: 1) the information captured by the tokens is limited (it misses a lot of diversity across iEEG signals and has a weak correlation to sleep scoring, for example); 2) the evaluation of tokens cannot be solely based on their ability to predict the future, but must also incorporate the information about the final task (e.g., sleep scoring). As a solution, we propose to replace the tokenization process with a direct feature learning task that has an explicit link to the final objective (e.g., sleep scoring). The main goal is to build features that allow to make predictions about the future state of the brain.

Study 2. Data Analysis. One of the main obstacles to this objective is the lack of real data for closed-loop systems. We explored several options, but either some of the available data showed limited correlation between the stimulus and the sleep scoring (so it could not be used in a closed-loop fashion) or the dataset was not large enough to train deep learning models. Currently, it is necessary to wait for a large closed-loop dataset to be built (this is an effort that, for example, the team of Prof Tzovara is driving). One immediate issue with small datasets is that a model built on such dataset does not work on new data. This is due to the high variability of annotation from one hospital to another and from patient to patient. The capability of a model to work across datasets is called generalization and we found it to be the next priority to enable the use of as much data as possible (essential with data scarcity problems). Towards this purpose we have been working on reducing the gap between the classification performance across patients and this led to a new self-supervised learning task that is biologically inspired (work published at GCPR2020); the idea is that different parts of the brain use phase amplitude correlation in different frequency bands to communicate to one another. We found that these correlations generalize across subjects despite differences (e.g., pathologies or other factors). We are currently investigating meta-learning as a more principled way to generalize across datasets. This is an important component to scale-up deep learning on EEG given the heterogeneity of the data available across different research groups. The extension of that would be to build features that generalize to predicting future sleep scores. This would be a first essential building block for the closed-loop system. If time allows and the closed-loop dataset will be ready, it might be possible to complete some of the components of the closed-loop system.

B14. Cognitive Modelling (Walter Senn)

The goal of the Computational Platform was to design novel computational tools that advance sleep research across the entire IRC. We focused our endeavors along three dimensions: (a) in data analysis and storage: this concerns the use of cutting-edge techniques, such as deep learning, to analyse (i)EEG data and surrogates in the context of sleep research (SP1 & 2); (b) in designing novel computational models: here we use concepts from artificial neural networks and provide a mechanistic understanding of the neural computations that take place during sleep, e.g. related to memory semantization or dreaming (SP3); (c) in education: we provided computational support in data analysis in any groups that need it, across the entire IRC. To achieve these goals, we have been organizing regular meetings between experimental and theoretical groups, which have given rise to new collaborations and inter-disciplinary projects. These meetings have been the ground for creating a new 'Sleep Neuromodulation Platform', whose goal is to unite and homogenize subprojects of the IRC working with closed-loop stimulation.

The Senn lab was engaged in (b) and (c) of the Computational Platform summary above. The goal of building a unifying computational model of sleep that assigns cognitive functions to non-REM

and REM sleep was achieved (b). Likewise, the goal of jointly organizing and running the Computational Platform with scientific spin-offs in experimental groups was achieved (c).

Project highlights

(b) Our project aims to understand the cognitive functions of sleep, and rebuild these functions in neuronal networks. We both seek for a better understanding of sleep in the human brain, and for extracting new principles to improve models of cognition and artificial intelligence. Our hypothesis was that the two phases of sleep, non-REM and REM sleep, represent a biological version of generative adversarial networks (GANs) that lay at the root of the unprecedented success of modern artificial intelligence. We formulated a new functional model of sleep, characterized as Perturbed and Adversarial Dreaming (PAD, Fig. 11), that shares many features of the human sleep and that is competitive with models for object recognition in artificial intelligence.

The PAD model offers a functional distinction between non-REM and REM dreams. In non-REM sleep, individual episodic memories are recalled from the hippocampus and consolidated in a cortico-hippocampal loop. In REM sleep, multiple memories are recalled and creatively mixed with other cortical activity. These creative mixes during REM train the brain to semantize new sensory inputs to which the network was not exposed so far. We show that both type of non-REM and REM dreaming improve the cortical representations of objects, and help to recognize objects presented in varied appearances and in new environments. The model also offers a framework to understand bottom-up and top-down cortical information processing and its interactions during wakefulness and sleep. More generally, the model shows how generative adversarial networks (GANs), so far considered to be mainly a smart method in artificial intelligence, can actually be implemented by cortical circuits, and possibly by self-learning neuromorphic hardware. The paper is in review at eLife (Deperrois et al., 2nd round, https://arxiv.org/abs/2109.04261), and so far produced wide interest.

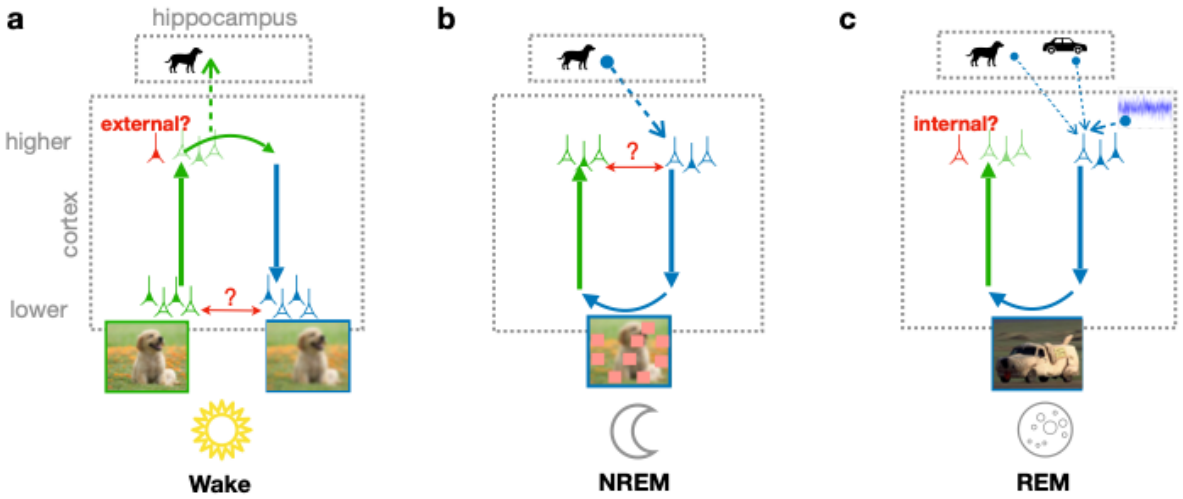


Figure 11. Perturbed and Adversarial Dreaming (PAD): the new computational model explains memory semantization during wake, non-REM and REM sleep. **A.** During wakefulness, sensory input is encoded in a forward stream (green) and is learned to be classified as 'external' (red). The sensory input is also learned to be re-created out of the abstract cortical representation (blue, red question sign). **B.** During non-REM sleep, the abstract episodic memory is played back from the hippocampus to the higher cortical area (dashed arrow). It produces a perturbed sensory activity that is learned to be matched in with the original higher representation (red question sign). **C.** During REM sleep, different abstract hippocampal and cortical memories are mixed (e.g. a dog and a car), creating a corresponding sensory activity (a doggy car). The quality of this 'adversarial creation' is improved until the encoding network erroneously classifies the sensory activity as ` external'. This generates creative, but still realistic dreams that help to classify objects in new environments during wakefulness.

(c) Our lab was engaged in providing educational and technical support for other groups. Various PIs with their involved group members regularly met for scientific report meetings at the Institute of Physiology (mainly Tzovara, Favaro, Adamantidis, Nissen, Henke, König and Senn; roughly tri-monthly, less after the lock-down). At these meetings, group members presented their scientific progress, and technical issues were extensively discussed. Group members bilaterally continued discussions, leading to various collaborations between theory and experimental groups (see also reports of A. Tzovara, P. Favaro and C. Nissen). From the Senn lab, N. Deperrois teamed up with the Adamantidis lab, and B. Ellenberger teamed up with the Nissen lab. Here are two highlights from the collaboration with the Nissen lab:

(c1) Based on ideas emerged during the platform meetings, C. Nissen and collaborators implemented a slow-wave EEG detection algorithm, paired with an acoustic stimulation that suppresses the slow-wave, without awakening the subjects. B. Ellenberger supported K. Fehér in the design and implementation of the randomized acoustic stimulation that led to a patent application (see below). A paper is in preparation.

(c2) C. Nissen's hypothesis states that in patients with major depression disorder the synaptic down-regulation during sleep would be too strong. We therefore set out to quantify the synaptic down-regulation during sleep using intra-cortical EEG traces (from epilepsy patients, made available by K. Schindler). We simulated a recurrent network of 'visible' and 'hidden' nodes, with target activities of the visible nodes being identified by the iEEG traces. The synaptic connection strengths of the network were adapted (by backpropagation through time) until the iEEG traces were best reproduced. Then the total absolute strengths of the network was extracted. This was done for time windows of several minutes, distributed across the sleep. We found that our best-fitted networks in fact decreased their total connection strength with progressing stages of the slow-wave-sleep. These results confirm G. Tononi's synaptic homeostasis hypothesis by novel modeling techniques. The project was accomplished with the help of a master student at the University of Applied Sciences (Jan Segessemann, but more data and controls are required for a publication).

C. FURTHER ACTIVITIES AND OUTREACH

C1. NeuroTec

Several PIs of the IRC Decoding Sleep belong to the core team of the newly founded NeuroTec at Sitem-Insel (https://www.neuro-tec.ch) which was officially opened in September 2021. This innovative platform provides IRC researchers with the crucial opportunity to collaborate not only with other academic research groups such as the Centre Suisse d'Electronique et de Microtechnique (CSEM) and the ARTORG Center, but also with industrial partners in order to develop, test and validate new technological approaches for the diagnosis, monitoring and treatment (e.g. using close-loop approaches) of sleep-wake and related disorders at home (tele-medicine).

The IRC sponsored Sleep Monitoring Study (SMS) is conducted together with the ARTORG Center. A collaboration, which has been promoted by the IRC and NeuroTec and led to the incorporation into the SMS of two newly developed CSEM devices for validation in sleep assessment. A follow-up clinical trial (externally funded) is already in the planning stages with the ultimate goal of launching those devices on the market. Furthermore, the group of A. Tzovara has relocated to NeuroTec, bringing groups from different IRC clusters (computational and clinical) in closer proximity, facilitating exchange and strengthening interdisciplinary and public-private collaborations. At the

same time, the NeuroTec infrastructure with EEG sleep labs, and the NeuroTec loft (see Figure 12) strongly benefits their research projects.

Figure 12. The NeuroTec loft is an instrumented apartment that allows to assess patients and novel devices under real world conditions. Here, marker-free motion tracking is demonstrated. The living room (a,d) and kitchen (e) are equipped with 13 cameras, which are as accurate as to then allow to fit a 54-point skeleton model onto the test-person's body (b,c), enabling high-precision assessment of movements. (Schindler et al., 2021).

C2. Swiss Sleep House Bern

Sleep House is a newly created unit in Bern which has the following main goals:

1. Offer a simple/rapid triage of sleep disorders in the general population ("walk-in clinic")
2. Foster the implementation of home-(tele-) sleep diagnostics
3. Secure the chronic care of patients with sleep-wake disorders,
4. Promote sleep health (and education) in the general population

The Sleep House is to be considered as an additional "player" in the Bernese Sleep network which includes the existing sleep-wake laboratories (including a newly founded Sleep-Motion-Lab at the Institute of Psychology), the center for experimental neurology/sleep (ZEN), and NeuroTec (see Figure 13). The novelty of the sleep house consists on the one hand in the use of novel technologies to assess sleep-wake and related disorders (using also ambulatory devices such as wearables and nearables previously validated in the Neurotec), and on the other hand in the involvement of new actors in their management such as general practitioners (of the BIHAM and outside), social and preventive scientists (of the ISPM), biotechnologists, psychologists and other health professionals.

The creation of this platform was approved by the Insel-Gruppe in November 2021 and will be officially launched in the summer of 2022.

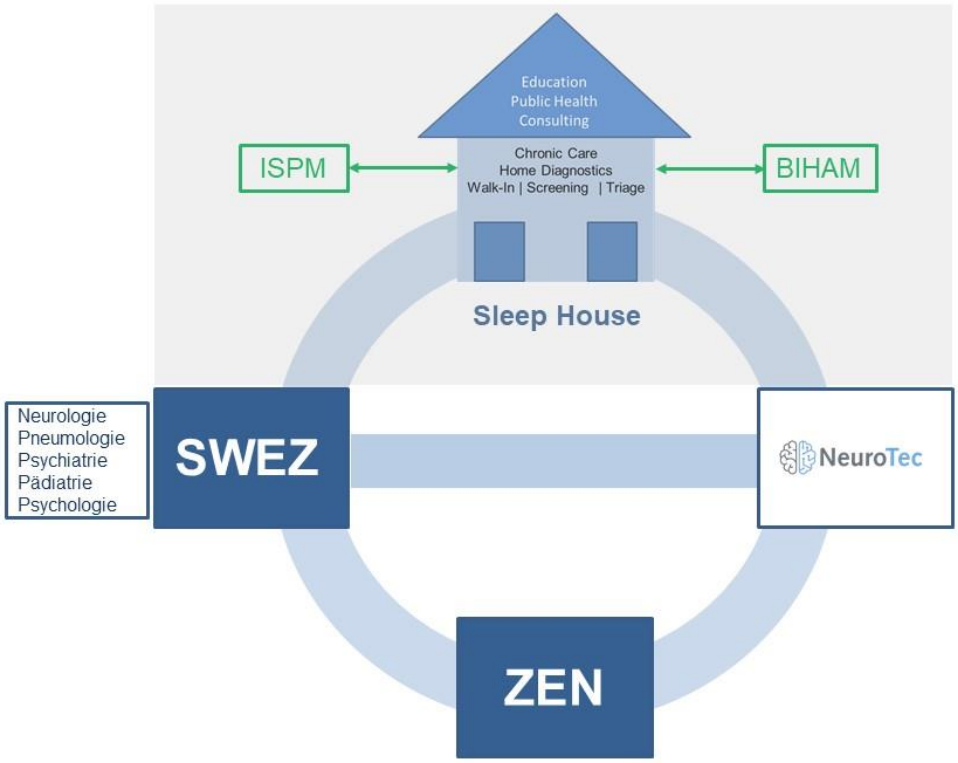


Figure 13. The Swiss Sleep House Bern as new "actor" of the Bernese Sleep Scene will be linked with the already existing platforms including traditional sleep-wake laboratories (SWEZ), the center for experimental neurology/sleep (ZEN) and the newly launched NeuroTec. (ISPM: Institute of Social and Preventive Medicine; BIHAM: Bernese Institute of Family Medicine).

Multiple PI and collaborators of the IRC and other people who are currently outside the IRC are involved in the Sleep House, including C. Bassetti, A. Vorster, and S. Duss (Neurology), K. Brill, T. Geiser (Pulmonology), C. Nissen (Psychiatry), T. Berger (Psychology), O. Franco (ISPM), N. Rodondi, R. Auer (BIHAM), C, Maya-Massetti (Pharmacy).

The IRC involvement at Sleep House will specifically focus on providing:

- Education of health professionals, biologists and psychologists in the field of sleep medicine in conjunction with the Academy of Sleep and Consciousness (see section C3)
- Information of the general public on sleep health and medicine (citizen science)
- Development of tele-sleep medicine, including research in collaboration with NeuroTec and the Sleep Bern Cluster

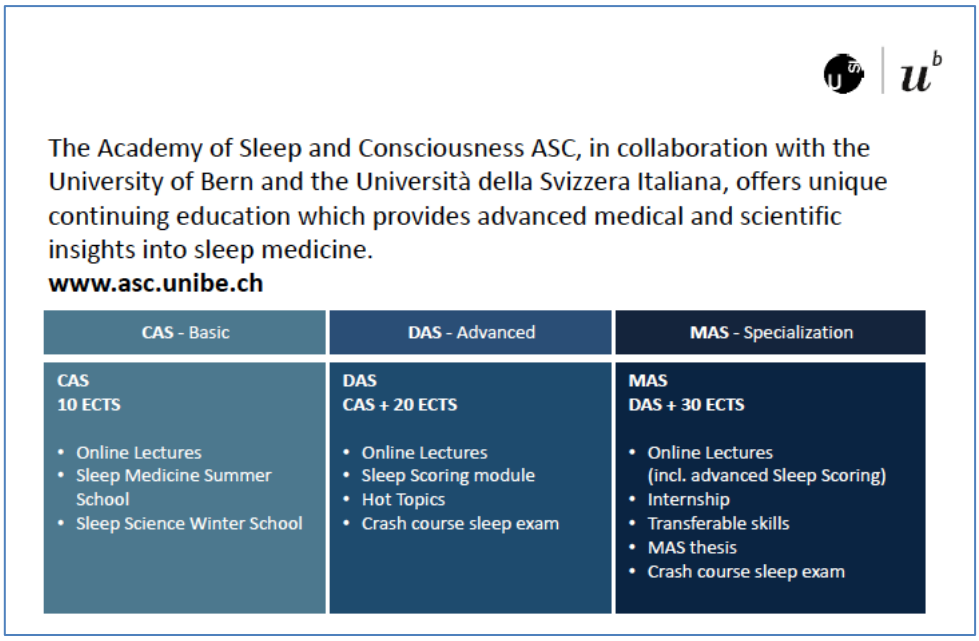
C3. Sleep Motion Lab

The Institute of Psychology is equipped with a human motion platform (MOOG) for experimental research (https://www.kog.psy.unibe.ch/forschung/labors/moog_lab/index_ger.html). So far, this device has been used for perception research (e.g., vestibular threshold testing) in upright test subjects. A bed-like structure is currently designed that can be mounted on the motion chair. This will make it possible to apply motion profiles when people are in the horizontal position, including during sleep. In addition to this, we have developed a new software: https://gitlab.com/KWM-PSY/platform-commander. PlatformCommander will not only control the motion profile (direction, duration, frequency etc.), because it can be interfaced with EEG, virtual reality, galvanic stimulation etc. This has the advantage that the motion profile can adapted depending on the person's position

on the bed. Some people prefer sleeping on the side while as others sleep in the supine position. Or they change position during sleep. Head motion can be tracked and it is interfaced with PlatformCommander so that the platform's motion profile is adaptive and therefore remains constant in head-fixed coordinates. We are not the first to investigate the use of body motion during sleep and its potentially beneficial impact on sleep architecture, but we have - to our knowledge- the best suitable equipment to thoroughly investigate the underlying mechanisms. Previous studies used different experimental paradigms and motion profiles, which is to a large extent caused by restrictions of the available technology. We can provide any type of motion (x,y, z-translations, and pitch, roll and yaw rotations), The knowledge ascertained during the four years of IRC in combination with the expertise on motion perception has brought us into the position to well design studies to investigate the impact of motion on sleep in order to exploit its potential in a wide field of applications, ranging from sleep quality, memory consolidation to fall prevention in old adults. The new laboratory is located at the Institute of Psychology, and it will attract Master students, PhD students, and Post-Docs for carrying out research projects. The software is open source and the group of Fred Mast has recently been published it in the Journal Software X (2022): https://www.sciencedirect.com/science/article/pii/S235271102100176X.

C4. Sleep Master Bern

Another important endeavor which sees the involvement of multiple members of the IRC Decoding Sleep is the revised Sleep Master Bern, formerly known as the Master of Sleep and Consciousness (launched by the University of Bern and Università della Svizzera Italiana in collaboration with 13 other partner Universities). After thorough evaluation, this master underwent an in-depth revision in order to offer in the near future a better modularization of the courses/offer, new top-trend topics and by going completely online to target a larger audience, also abroad. The new "Sleep Master" will foster the visibility of sleep medicine and research in Bern to a larger international audience. This program provides the opportunity to teach and train the next generation of sleep health professionals and researchers.



C5. Workshops, Congresses, and Media

As in previous years, IRC researchers have participated in 2021 at many international and national conferences and congresses to which they contributed over 30 talks and numerous posters. In addition, many lectures as part of semester courses, lecture series, and summer or winter schools were given. Some group leaders were also involved in the organization of those events.

In 2021 several congresses were organized by PI's of the IRC including the following international conferences:

The World Sleep Forum on Sleep and Neurodegeneration

The Sleep Medicine Summer School in Grenoble

European Master Class and Narcolepsy Day

On November 10, 2021, as part of the 25th annual Sleep-Wake-Epilepsy Days in Bern, a full day was dedicated to the research of the IRC "Decoding Sleep". Two invited guest speakers from Israel and the United States were a great addition to our diverse scientific program, covering all three clusters of the IRC.
We have seen one of the largest crowds in our history with over 100 participants, some of which travelled internationally, others joined us from Zürich, Basel and Geneva. This reflects the large interest in our research and shows the importance of the IRC in the field of sleep research, and neighboring disciplines. In their effort to bring their science and research to an even larger non-scientific audience, IRC group leaders also had several media appearances. With radio, online media, social media, and print media, our research was covered over 60 times.

Mittwoch, 10. November, 09.00–15.30 Uhr

IRC* Decoding Sleep Symposium

Inselspital Bern, Hörsaal Langhans

Programm

09.00	**Welcome Address** Claudio L. Bassetti
09.05–09.30	**Optical dissection of sleep circuits & functions** Antoine Adamantidis
09.30–10.15	**Sensory disconnection during sleep and sleep-like states** Yuval Nir
10.15–10.45	Coffee Break
10.45–11.15	**Sleep in adolescents with major depressive disorder** Leila Tarokh
11.15–12.00	**Rocking is not Rolling: Perspectives for Motion Devices in Sleep Research** Fred Mast
12.00–12.45	Lunch
12.45–13.15	**Computational approaches for studying sleep and pathological loss of consciousness** Athina Tzovara
13.15–14.00	**Sleep and other Disorders of Consciousness** Melanie Boly
14.00–15.30	Poster Session and Coffee

C6. Internal Collaborations

The IRC Decoding Sleep has provided a platform for exchange and collaboration to all involved groups. Central to this was the idea to bring groups from different faculties and disciplines together to promote interdisciplinary research. The large number of collaborations across groups stands as evidence that this has been a great success:

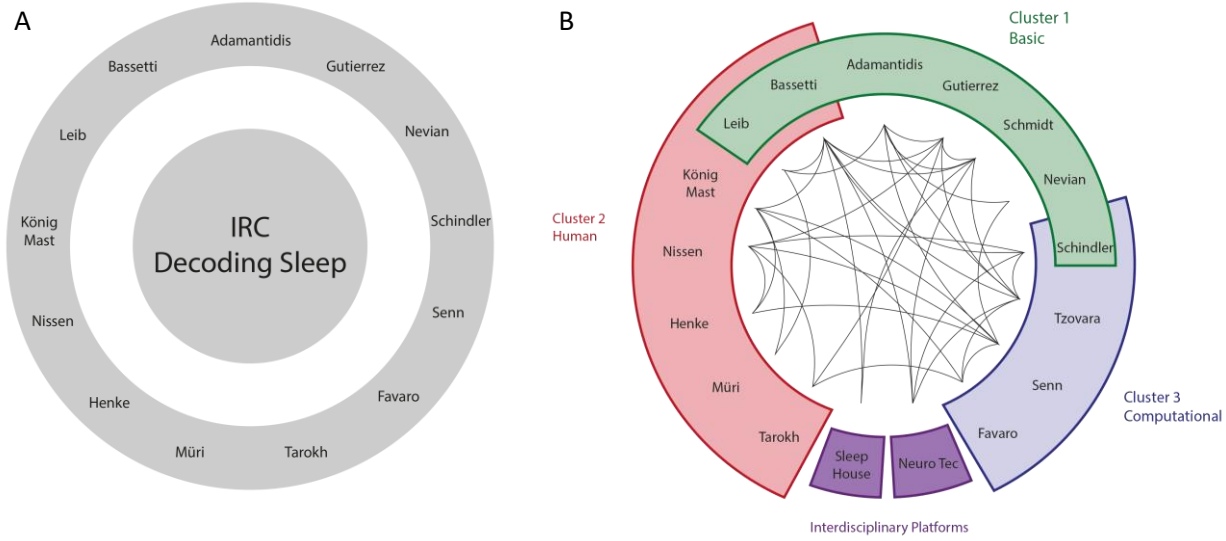


Figure 14. Internal Collaborations of the IRC – transformation of individual groups into a highly inter-connected network. **A.** Before the start of the IRC: individually operating groups intended to come together in the IRC which should serve as a platform for exchange and collaboration. **B.** After the first 4 years of the IRC: the groups have grown together, three clusters and many collaborations have formed.

C7. Collaborations Outside the University

The IRC Decoding Sleep has established itself as a landmark research consortium in the Swiss sleep research community. To date, no sleep research consortium worldwide covers a comparatively large range of disciplines involved. A number of new national and international collaborations were established in 2021, while others were strengthened and expanded.

Antoine Adamantidis: S. Brown, University of Zurich, Y. Nir, University of Tel Aviv, Israel; M.L. Lörincz, University of Szeged, Hungary
Katharina Henke: N. Axmacher, Bochum University, Germany
Thomas Nevian: M. X. Cohen, Radboud University, Netherlands
Markus Schmidt: P.H. Luppi, University of Lyon, France; R. Fronczek, University of Leiden, Netherlands
Athina Tzovara: M. De Lucia, CHUV, Lausanne, L. Imbach, University of Zurich; K. Schindler, University of Bern; CSEM; Neuchâtel, M. Baud, University of Bern
Claudio Bassetti: U. Kallweit, University of Herdecke, Germany; G. Plazzi, University of Bologna, Italy; T. Mann, University of Munich, Germany; F. Sallusto, ETH, Zurich
Paolo Favaro: L. Fiorillo and F. Faraci, SUPSI, Lugano
Carolina Gutierrez: K. Do, University of Lausanne; I. Goshen, University of Jerusalem, Israel
Fred Mast: Wang Gu, Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China
Stephen Leib: Daniel RUZEK, Institute of Parasitology, Biology Centre, ASCR, v.v.i. České Budejovice – Czech Republic

C8. IRC Journal Club

For the past three years (2019-2021), the IRC has held a monthly Journal Club for its members, which has also attracted attendance from students outside of the IRC. This Journal Club brought together our students and researchers from different disciplines, faculties, and clusters. Each Journal Club, two students from different clusters prepared a paper to be discussed and led the discussion. Their supervisors provided senior level support. On several instances we received the feedback that these interactions were invaluable in different ways:

- Provided the time and grounds to get to know and interact with other researchers
- Helped to establish a common vocabulary and understanding about each other's research
- These interactions finally led to new collaborations and culminated in publications

C9. Measures to Promote Young Scientists and Gender Equality

The first PhD students of the IRC "Decoding Sleep" have successfully completed their studies and graduated. Most of the remaining students will defend their theses in 2022 with the exception of two, where additional severe circumstances further delayed the project in addition to the Covid pandemic. We are very delighted, that our first PhD student has already secured a postdoc position at the University of Zürich and that the IRC-affiliation was key for one postdoc to acquire a prestigious advanced postdoc position at the University of Tübingen, Germany.

Four new PhD students (Viberti: rodent model of narcolepsy; E. Wenz, Fregolente: SPHYNCS; PhD between Nissen and Gutierrez) were acquired (and mostly funded by grants independent form the IRC)

A number of bachelor, master students and research assistants had their first exposure to research in IRC project.

Four PI of the IRC have completed their habilitation: Carolina Gutierrez (2021), Kathrin Brill (2021), Leila Tarokh (submitted), and Markus Schmidt (submitted).

Panagiotis Bargiotas, who lead a subproject during the first half of the IRC, was called as assistant professor at the University of Nicosia, Cyprus.

The nomination of Christoph Nissen as full professor of psychiatry at the University of Geneva

The consolidation of Athina Tzovara to tenure track professor at the University of Bern with a double affiliation between the Faculty of Science and the Faculty of Medicine has been approved by the University of Bern in fall 2021.

Special emphasis has also given to promoting female researchers. Half of the IRC members are female, amongst the PhD students, two thirds are female. Several of our PhD students paused their studies for maternity leave, which was supported by the IRC and the supervising PIs. In the same vein, the members of the IRC are very much aware of this topic and one of the PIs (Athina Tzovara) contributed to a seminal publication in the Journal *Neuron (lLorens, Tzovara, Bellier et al., 2021), entitled "Gender bias in academia; A lifetime problem that needs solutions".*

Sebastian Ott was clinically promoted to head of pulmonology at the University Spital / Claraspital Basel.

In the future, we are planning to include an advanced female researcher in the advisory board.

D. PUBLICATIONS

D1. Accepted Publications

Over the four years the researchers of the IRC consortium published over 100 publications related to the IRC project. The full list can be found as attachment. Additional publications are expected for 2022, as more projects will be completed. This also applies to IRC groups, which were not traditionally involved in sleep research before joining the IRC, and which resulted in a longer preparatory phase for them.

The top 15 publications are listed below:

Adamantidis, A. R., Herrera, C. G. & Gent, T. C. Oscillating circuitries in the sleeping brain. Nature Reviews Neuroscience 20, 746-762 (2019).

Alnes, S. L., De Lucia, M., Rossetti, A. O. & Tzovara, A. Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma. NeuroImage 245, 118638 (2021).

Baillieul, S., Dekkers, M., Brill, A.-K., Schmidt, M. H., Detante, O., Pépin, J.-L., Tamisier, R. & Bassetti, C. L. Sleep apnoea and ischaemic stroke: current knowledge and future directions. The Lancet Neurology 21, 78-88 (2022). (Review)

Bandarabadi, M., Herrera, C. G., Gent, T. C., Bassetti, C., Schindler, K. & Adamantidis, A. R. A role for spindles in the onset of rapid eye movement sleep. Nature Communications 11, 1-12 (2020).

Bassetti, C. L., Kallweit, U., Vignatelli, L., Plazzi, G., Lecendreux, M., Baldin, E., Dolenc-Groselj, L., Jennum, P., Khatami, R. & Manconi, M. European guideline and expert statements on the management of narcolepsy in adults and children. **European Journal of Neurology** 28, 2815-2830 (2021).

Castegnetti, G., Tzovara, A., Khemka, S., Melinščak, F., Barnes, G. R., Dolan, R. J. & Bach, D. R. Representation of probabilistic outcomes during risky decision-making. **Nature Communications** 11, 1-11 (2020).

Facchin, L., Schöne, C., Mensen, A., Bandarabadi, M., Pilotto, F., Saxena, S., Libourel, P. A., Bassetti, C. L. & Adamantidis, A. R. Slow waves promote sleep-dependent plasticity and functional recovery after stroke. **Journal of Neuroscience** 40, 8637-8651 (2020).

Gutierrez-Herrera, C. G., Girard, F., Bilella, A., Gent, T. C., Roccaro-Waldmeyer, D. M., Adamantidis, A. & Celio, M. R. Neurons in the Nucleus papilio contribute to the control of eye movements during REM sleep. **Nature Communications** 10, 1-11 (2019).

Komagata, N., Latifi, B., Rusterholz, T., Bassetti, C. L., Adamantidis, A. & Schmidt, M. H. Dynamic REM sleep modulation by ambient temperature and the critical role of the melanin-concentrating hormone system. **Current Biology** 29, 1976-1987. e1974 (2019).

Latorre, D., Kallweit, U., Armentani, E., Foglierini, M., Mele, F., Cassotta, A., Jovic, S., Jarrossay, D., Mathis, J., Zellini, F, Bassetti CL*, Sallusto F*. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. **Nature** 562, 63-68 (2018) *co-shared last authors

Markovic, A., Kaess, M. & Tarokh, L. Environmental factors shape sleep EEG connectivity during early adolescence. **Cerebral Cortex** 30, 5780-5791 (2020).

Nissen, C., Piosczyk, H., Holz, J., Maier, J. G., Frase, L., Sterr, A., Riemann, D. & Feige, B. Sleep is more than rest for plasticity in the human cortex. **Sleep** 44, zsaa216 (2021).

Ruch, S. & Henke, K. Learning during sleep: a dream comes true? **Trends in Cognitive Sciences** 24, 170-172 (2020). (Review)

Llorens, A., Tzovara, A., Bellier, L., Bhaya-Grossman, I., Bidet-Caulet, A., Chang, W. K., Cross, Z. R., Dominguez-Faus, R., Flinker, A., Fonken, Y., Gorenstein, M., Holdgraf, C., Hoy, C., Ivanova, M., Jimenez, R., Jun, S., Kam, J., Kidd, C., Marcelle, E., Marciano, D., Martin, S., Myers, N., Ojala, K., Perry, A., Pinheiro-Chagas, P., Riès, S., Saez, I., Skelin, I., Slama, K., Staveland, B., Bassett, D., Buffalo, E., Fairhall, A., Kopell, N., Kray, L., Lin, J., Nobre, A., Riley, D., Solbakk, A., Wallis, J., Wang, X., Yuval-Greenberg, S., Kastner, S., Knight, R. & Dronkers, N. Gender bias in academia: A lifetime problem that needs solutions. **Neuron** 109, 2047-2074 (2021).

Züst, M. A., Ruch, S., Wiest, R. & Henke, K. Implicit vocabulary learning during sleep is bound to slow-wave peaks. **Current Biology** 29, 541-553. e547 (2019).

D2. Manuscripts made accessible on Preprint Repositories

A number of publications are in the reviewing process and will shortly be published. Meanwhile, some have been made available to the research community by sharing them on preprint repositories such as bioRxiv. Those manuscripts will not be listed here, but in case they have been submitted to repositories, they are available in the appendix.

E. ADDITIONAL FUNDING

Over the four years the researchers of the IRC consortium have successfully acquired additional funds in 2021, totaling CHF over 12.9 Million CHF. The full list can be found as attachment. The top grants (> 100'000 CHF) are listed below:

Grant	Duration	Applicant	Sum
EU Horizon 2020: Human Brain Project	2020 - 2023	W. Senn	2'591'850
SNF Eccellenza	2022 - 2027	M. Baud	1'700'000
SNF Project Grant	2019 - 2023	T. Nevian	1'008'000
IRC Matching Funding (multiple sources, see final report)	2021 - 2024		870'000
SNF: SPHYNCS Study	2019 - 2023	C. Bassetti	759'000
SNF: Sleep Neurophysiology: A Window onto Adolescent Mental Health		L. Tarokh (Co-Applicant)	702'436
SNF Project Grant	2020 - 2024	A. Adamantidis	700'000
SNF: 'Sensory predictions in the human brain	2020 - 2023	A. Tzovara	497'413
SNF Sinergia	2018 - 2022	W. Senn	488'000
University of Bern / Multidisciplinary Center for Infectious Diseases (MCID)	2022 - 2024	S. Leib	473'926
NIH: Biopsychosocial Factors Impacting Ethnic/Racial Differences in Adolescent Sleep Regulation		L. Tarokh	457'515
SNF: neural basis of sleep perception		C. Nissen	400'000
Synapsis foundation project on sleep and cognition in aging		C. Nissen	300'000
Center for Cognition, Learning, and Memory & Swiss Graduate School for Learning and Memory: PhD Salary		F. Schmidig / K. Henke	250'000
Fondation Pierre Mercier pour la science	2020 - 2023	A. Tzovara	235'000
SISF: Project / Infrastructure Grant	2020	F. Mast	200'000
PhD Grant	2020 - 2024	E. Wenz / C. Bassetti	200'000
Genolier: Sleep House (MD and lab tech)	2022 - 2023	C. Bassetti	200'000
SISF: Project / Infrastructure Grant	2020	S. Leib	135'000
Jazz Pharmaceuticals: SPHYNCS Study	2020 - 2022	C. Bassetti	105'000

F. SUSTAINABILITY

F1. Sustainable Continuation of IRC During and Beyond Extension Phase

Research

Two ERC applications and several new SNF proposals have been submitted and two Sinergia applications are currently in preparation. Two PI's of the future IRC leadership (Antoine Adamantidis, Athina Tzovara) representing the three main clusters will prepare a new NCCR submission.

Platforms

The NeuroTec has a financial plan, which has self-sustainability through public and private sources within the next 5 years. The Swiss Sleep House also has a financial plan which is based on clinical activities within the next 5 years. The soon to be launched Sleep Motion Lab at the Department of Psychology will be supported by the Technology Platform of the Human Sciences Faculty, and the Institute of Psychology.

Academic positions

Athina Tzovara has a double affiliation between the Faculty of Science and the Faculty of Medicine, and her team is affiliated with NeuroTec

L. Tarokh will take over in the Psychiatry Department (UPD) the coordination responsibilities of sleep research and teaching previously held by C. Nissen.

Education

The Postgraduate Sleep Master (ASC, see above) is planned to be offered (also) as a virtual program and to be financed from 2023 exclusively by study fees. The European Sleep Foundation which has supported the creation of the Master will continue to ensure the costs for the program coordinators.

The Bachelor in Neuroscience (30 ECTS) offered by the Human Sciences Faculty is currently evaluated, and it will continue to be highly attractive field of study with almost 400 students enrolled. Several researchers from the IRC Decoding Sleep provide lectures and seminars (e.g., L. Tarokh, W. Senn, A. Adamantidis, T. Nevian, K. Henke, F. Mast, T. König)

Communication

The finances for communication (e.g. webpage, newsletters, others) will be covered by the new Sleep Bern initiative (see above) to be launched in 2022.

F2. New academic positions

Double affiliations

In addition to the double affiliation of A. Tzovara with the Faculties of Medicine and Science further double affiliations with the Faculty of Human Sciences are currently in discussion.

New appointments in sleep-related fields

Maxim Baud of the Department of Neurology, who is increasingly involved in the IRC with his research on circadian determinants of epileptiform activity (see e.g. Baud M, Nature Commun 2018; Karoly et al., Nature rev Neurol 2021) and has recently received an SNF Eccellenza. During the past months, he has been well integrated into the IRC network and now has ongoing collaborations with multiple IRC groups (K. Schindler, A. Tzovara, A. Adamanditis).

T. Berger, who is increasingly involved in the IRC with his research on tele- and e-mental health, has received the prestigious Benoist prize (2021). First collaborations with him have already started as evident in several shared publications and the co-supervision of a PhD student from Russia.

The Department of Neurology will open in January 2022 a new Professor position in the field neurodegenerative disease who is expected to collaborate within a new research cluster in Bern on sleep and dementia/neurodegeneration (S. Klöppel, R. Wiest, S. Saxena, A. Adamantidis, A. Rominger, K. Schindler).

The Psychiatric Department (UPD) at the Medical Faculty will open two new positions in 2023. A continuation and potentially strengthening of sleep research in psychiatry is expected.

The Institute of Social and Preventive Medicine at the Medical Faculty will open in 2023-24 few new positions. Discussions about the creation of a new position in Brain (and Sleep) Health are currently discussed.

The Human Sciences Faculty has created two Departments with health-related topics: Health Science at the Institute of Sport Science (C. Nigg), and Health Psychology and Behavioral Medicine at the Institute of Psychology (J. Innauen), thus strengthening the University's priority area of Health and Medicine. These topics open new possibilities for sleep related research, and they enlarge the range of research groups. At the Institute of Psychology, several positions will be filled in 2026/27, and it is in discussion whether neuroscience will be one of the areas that need more emphasis, and thereby complement research activities in other faculties.

Shared discussions across faculties will be important to optimize the outcome for the University, strengthen local networks and to minimize the chance of stand-alone projects with none or little interdisciplinary outreach. The IRC Decoding Sleep has undertaken lots of efforts to increase exchange between faculties, and these interactions had sustainable impact.

F3. Technology Transfer from Bench to Bed – How IRC Research Changes Patient Care

The recently inaugurated **NeuroTec** platform at Sitem-insel (see also above) will offer, in collaboration with the ARTORG, a crucial opportunity to collaborate not only with other academic research groups such as the Centre Suisse d'Electronique et de Microtechnique (CSEM) and the ARTORG Center, but also with industrial partners in order to develop, test and validate new technological approaches for the diagnosis, monitoring and treatment (e.g. using close-loop approaches) of sleep-wake and related disorders at home (tele-medicine).

The IRC Groups Nissen, Henke, and Senn have developed a **closed-loop stimulation approach** (see also above) to selectively suppress slow-wave sleep in patients with major depression.

The **Swiss Sleep House Bern** which will be launched in 2022 will promote the education of health professionals, biologists and psychologists in the field of sleep medicine and research. In addition, the sleep house will foster the use of tele-sleep medicine approaches, including research in collaboration with NeuroTec and the entire Sleep Bern Cluster.

APPENDIX 1: COMPLETE PUBLICATION LIST

Appendix 1.1: Peer-Reviewed Publications: Published and Accepted

1 Adamantidis, A. R., Herrera, C. G. & Gent, T. C. Oscillating circuitries in the sleeping brain. Nature Reviews Neuroscience 20, 746-762 (2019).

2 Adamantidis, A. R., Schmidt, M. H., Carter, M., Burdakov, D., Peyron, C. & Scammell, T. E. A circuit perspective on narcolepsy. Sleep 43, zsz296 (2020).

3 Aellen, F. M., Göktepe-Kavis, P., Apostolopoulos, S. & Tzovara, A. Convolutional neural networks for decoding electroencephalography responses and visualizing trial by trial changes in discriminant features. Journal of neuroscience methods 364, 109367 (2021).

4 Alnes, S. L., De Lucia, M., Rossetti, A. O. & Tzovara, A. Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma. NeuroImage 245, 118638 (2021).

5 Ancona, S., Faraci, F. D., Khatab, E., Fiorillo, L., Gnarra, O., Nef, T., Bassetti, C. L. & Bargiotas, P. Wearables in the home-based assessment of abnormal movements in Parkinson's disease: a systematic review of the literature. Journal of neurology, 1-11 (2021).

6 Baillieul, S., Dekkers, M., Brill, A.-K., Schmidt, M. H., Detante, O., Pépin, J.-L., Tamisier, R. & Bassetti, C. L. Sleep apnoea and ischaemic stroke: current knowledge and future directions. The Lancet Neurology 21, 78-88 (2022).

7 Bandarabadi, M., Boyce, R., Gutierrez Herrera, C., Bassetti, C. L., Williams, S., Schindler, K. & Adamantidis, A. Dynamic modulation of theta–gamma coupling during rapid eye movement sleep. Sleep 42, zsz182 (2019).

8 Bandarabadi, M., Herrera, C. G., Gent, T. C., Bassetti, C., Schindler, K. & Adamantidis, A. R. A role for spindles in the onset of rapid eye movement sleep. Nature communications 11, 1-12 (2020).

9 Bargiotas, P., Bargiotas, I., Debove, I., Lachenmayer, M. L., Vayatis, N., Schuepbach, W. M. & Bassetti, C. L. Sleep apnea syndrome and subthalamic stimulation in Parkinson's disease. Sleep medicine 86, 106-112 (2021).

10 Bargiotas, P., Debove, I., Bargiotas, I., Lachenmayer, M. L., Ntafouli, M., Vayatis, N., Schüpbach, M. W., Krack, P. & Bassetti, C. L. Effects of bilateral stimulation of the subthalamic nucleus in Parkinson's disease with and without REM sleep behaviour disorder. Journal of Neurology, Neurosurgery & Psychiatry 90, 1310-1316 (2019).

11 Bargiotas, P., Dietmann, A., Haynes, A. G., Kallweit, U., Calle, M. G., Schmidt, M., Mathis, J. & Bassetti, C. L. The Swiss Narcolepsy Scale (SNS) and its short form (sSNS) for the discrimination of narcolepsy in patients with hypersomnolence: a cohort study based on the Bern Sleep–Wake Database. Journal of neurology 266, 2137-2143 (2019).

12 Bargiotas, P., Lachenmayer, M. L., Schreier, D. R., Mathis, J. & Bassetti, C. L. Sleepiness and sleepiness perception in patients with Parkinson's disease: a clinical and electrophysiological study. Sleep 42, zsz004 (2019).

13 Bassetti, C. L. Sleep and stroke: A bidirectional relationship with clinical implications. Sleep medicine reviews 45, 127-128 (2019).

14 Bassetti, C. L., Adamantidis, A., Burdakov, D., Han, F., Gay, S., Kallweit, U., Khatami, R., Koning, F., Kornum, B. R. & Lammers, G. J. Narcolepsy—clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nature Reviews Neurology 15, 519-539 (2019).

15 Bassetti, C. L., Kallweit, U., Vignatelli, L., Plazzi, G., Lecendreux, M., Baldin, E., Dolenc-Groselj, L., Jennum, P., Khatami, R. & Manconi, M. European guideline and expert statements on the management of narcolepsy in adults and children. European journal of neurology 28, 2815-2830 (2021).

16 Bassetti, C. L., Randerath, W., Vignatelli, L., Ferini-Strambi, L., Brill, A.-K., Bonsignore, M. R., Grote, L., Jennum, P., Leys, D. & Minnerup, J. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. European respiratory journal 55 (2020).

17 Baud, M. O., Schindler, K. & Rao, V. R. Under-sampling in epilepsy: limitations of conventional EEG. Clinical neurophysiology practice 6, 41-49 (2021).

18 Bernasconi, C., Ott, S. R., Fanfulla, F., Miano, S., Horvath, T., Seiler, A., Cereda, C., Brill, A.-K., Young, P. & Nobili, L. SAS CARE 2–a randomized study of CPAP in patients with obstructive sleep disordered breathing following ischemic stroke or transient ischemic attack. Sleep medicine: X 2, 100027 (2020).

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Appendix 1.2: Publications on Preprint Servers

1 Acuña, M. A., Kasanetz, F., De Luna, P. & Nevian, T. Cortical representation of pain by stable dedicated neurons and dynamic ensembles. **bioRxiv** (2020).

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