



Meeting Report

2019 Annual Meeting of the Swiss Society for Sleep Research, Sleep Medicine, and Chronobiology (SSSSC)

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Received: 19 July 2019; Accepted: 22 July 2019; Published: 20 September 2019



We are pleased to present you with this Special Issue of *Clocks & Sleep*, the abstracts of the 2019 annual meeting of the Swiss Society for Sleep Research, Sleep Medicine, and Chronobiology (SSSSC), which took place in Fribourg, 27 and 28 June.

The 2019 meeting in Fribourg provided evidence-based education to advance the science and clinical practice of sleep medicine and sleep physiology, disseminated cutting-edge sleep and circadian research, promoted the translation of basic science into clinical practice, and fostered the future of the field by providing young clinicians and researchers with the opportunity to present their findings in talks and through posters, the abstracts of which can be found in this Special Issue.

Renowned international and national speakers provided comprehensive updates, educational workshops, and insights into novel scientific topics covering various areas of sleep research and sleep medicine. Special emphasis was given to the field of insomnia, sleep and cognition, sleep and development, oscillatory mechanisms, sleep apnea, and autoimmune disorders.

A data-flash and poster session allowed for the presentation of the latest results of current research. Most importantly, the meeting provided ample opportunities to bring together people to engage in discussions and plan clinical cases and scientific projects.

Taken together, we had an exciting, inspiring, and collaborative meeting in Fribourg!

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Session “Basic Science”

1. Waking Up during the Night—Timing of Microarousals in Relation to the Infralow Oscillation of Mouse NREM Sleep

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Background: Uninterrupted periods of sleep and wakefulness are an integral part of a healthy life cycle. However, brief awakenings also occur while being asleep. These are thought to appear randomly and are commonly considered as disruptive or even pathological elements of sleep. Furthermore, strategies to anticipate and prevent awakenings are currently missing. Here, we analysed the timing of microarousals in mouse non-rapid eye movement sleep (NREMS) in the light of a novel infralow oscillation that segregates NREMS into periods of fragility and continuity.

Methods: Using polysomnographic recordings, we determined infralow dynamics of sigma power (10–15 Hz) and microarousals. We used 6 h of total sleep deprivation to increase homeostatic sleep pressure, and 6 h- of selective REM sleep (REMS) deprivation using closed-loop feedback techniques to increase REMS pressure.

Results: We find that microarousals in mouse NREMS occur overwhelmingly time-locked during the fragility periods. When homeostatic sleep pressure was increased, fewer fragility periods were interrupted by microarousals. When only REMS pressure was augmented instead, fragility periods became primarily interrupted by transitions into REMS. Specifically, NREMS showed entries into REMS every ~50 or 100 s, thus coinciding with the periodicity of the infralow oscillation. Instead, the frequency of microarousals was diminished.

Conclusions: We conclude that the timing of microarousals is gated by the fragility periods of the infralow oscillation that constitute permissive windows for transitions out of NREMS, which can be allocated to NREMS–wake or NREMS–REMS transitions according to instantaneous pressures. These data provide a framework for the possibility of moment-to-moment assessments of sleep’s fragility to anticipate, and potentially protect, ill-timed awakenings.

Funding: No funding.

2. Standing Sentinel during Human Sleep: Continued Evaluation of Environmental Stimuli in the Absence of Consciousness

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Background: Previously, stimuli such as a subject’s own name (SON) or a familiar voice have been shown to be processed preferentially during wakefulness. SONs and negative prosody have been shown to continue being salient even during unconscious non-rapid eye movement (NREM) sleep stage N2. Here, we investigated stimulus processing during wakefulness and across all the sleep stages (i.e., NREM sleep stages N1, N2, N3, and REM sleep). Furthermore, we also investigated oscillatory sleep electroencephalography (EEG) phenomena, i.e., sleep spindles and slow oscillations (SOs), and how their occurrence and characteristics relate to stimulus processing.

Methods: The modulation of stimulus processing by stimulus salience was studied by means of evoked oscillatory responses (event-related de/synchronisation [ERS/ERD]) and event-related potentials (ERPs)

using high-density electroencephalography (EEG). Specifically, we varied stimulus salience on two dimensions: (i) subjective relevance and (ii) paralinguistic aspects of emotional relevance. To this end, we presented participants with SONs versus unfamiliar names (UNs) and additionally varied the familiarity of the voice, i.e., familiar versus unfamiliar voice (FV versus UFV).

Results: Analyses of ERS/ERD and ERPs reveal that the evaluation of voice familiarity continues during all of the NREM sleep stages, including N3 sleep and even REM sleep. Especially, UFV stimuli elicit larger responses in a 1 to 15-Hz range as well as larger K-complex-like responses, suggesting they continue being salient. Beyond this and contrasting earlier findings, we find that sleep spindles and the negative slope of SOs do not uniformly inhibit information processing, but inhibition seems to be scaled to stimulus salience.

Conclusions: The findings add to existing evidence for a “sentinel processing mode” of the human brain during sleep. This mode is characterised by the continued processing of environmental stimuli that may be followed by either an inhibitory sleep-protective response or awakening depending on the result of stimulus evaluation. Beyond this, it appears that even “transient oscillatory activity”, i.e., sleep spindles and slow oscillations, is sensitive to stimulus salience.

Funding: Konrad-Adenauer-Stiftung e.V. & Austrian Science Fund (FWF: W-1223, Y-777, J-4243)

3. Basal Forebrain Contributions to Brain State Regulation during Auditory Learning and Sleep

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Background: The basal forebrain (BF) projections play an important role in modulating neural network states, for example by enhancing cortical responsivity as well as contributing to wake/sleep regulation. The BF projections regulate cerebral cortical function by providing the major source of cholinergic as well as GABAergic and glutamatergic input to the neocortex.

Methods: Here, we aim to investigate the neuromodulatory influence of the BF on brain state regulation by combining optogenetic stimulation in the ventral pallidum of the BF with electrophysiology in the anterior cingulate cortex (ACC) in rats. To study the functional contribution of the BF projection system on learning behaviour, we developed an auditory discrimination paradigm. Rats learned to discriminate segments of different Fourier amplitude-matched classical music pieces using an operant conditioning paradigm.

Results: By optic BF activation (ChR2 general virus), our preliminary analyses revealed an increase in movement speed and impaired discrimination performance. By contrast, BF inhibition (Arch general virus) did not affect discrimination performance, but triggered a reduction in operant lever pressing. We also conducted sleep experiments, during which we manipulated the amount of non-rapid eye movement (NREM) sleep by BF optogenetics. We observed disturbed cortical slow wave activity associated with an increase in wakefulness following BF activation, whereas BF inhibition led to prolonged NREM sleep with elevated cortical delta oscillations.

Conclusions: Our findings shed new light on the role of the basal forebrain nucleus ventral pallidum in terms of regulating behaviour state, learning, and sleep.

Funding: Swiss National Science Foundation Doc.CH 168602.

4. Optimising Auditory Stimulation of Slow-Wave Sleep and Associated Memory Benefits

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Background: Closed loop auditory stimulation (CLAS) has repeatedly been shown to improve performance on a word pair association task. However, there is little evidence of whether this stimulation has similar effects on other memory tasks. We studied the effect of CLAS on two memory tasks: mnemonic similarity (MST) and serial reaction time (SRTT). Furthermore, we aimed to optimise CLAS by understanding the effect of varying the stimulation protocol upon ongoing oscillatory brain activity during S3 sleep. As such, stimulus duration was either 50 ms or 100 ms of pink noise. Meanwhile, the length of the inter stimulus interval (ISI) was varied between one, two and three slow oscillations.

Methods: Seventeen volunteers attended the lab for two nights, seven days apart. One night consisted of CLAS (STIM), the other consisted of no stimulation (SHAM). Stimulation was delivered during stage 2 and stage 3 sleep.

Results: Pattern separation scores in the MST became significantly worse overnight in both conditions. In STIM there was a smaller and less significant reduction in performance overnight, however, there was no significant difference between conditions. There was also no clear trend when stimuli were divided based upon their difficulty. Recognition memory showed similar results, however, the hardest stimuli to distinguish were significantly less poorly affected in STIM than SHAM. Interestingly, STIM showed a non-significant trend to being detrimental to the easiest stimuli to distinguish compared to SHAM. Overnight changes in SRTT were not significant between conditions, but a qualitatively larger increase in speed occurred in STIM. Reaction times in a psychomotor vigilance task decreased overnight in STIM but increased in SHAM; however, the difference was not significant. There was a non-significant trend for larger ERP in STIM nights when stimuli of 100 ms were used. There appeared to be little difference in ERP when ISI was varied.

Conclusions: Our results provide trend-level support for the idea that CLAS enhances performance on these tasks; however, more data is needed to establish whether this is significant. Electrophysiology results warrant further analysis to understand the wider impact on sleep.

Funding: This project was funded as part of a BBSRC PhD studentship.

5. Locus Coeruleus Noradrenergic Modulation of Primary Dorsal Thalamus Tunes the Infralow 0.02-Hz Oscillation of Mouse NREM Sleep

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Background: Non-rapid eye movement sleep (NREMS) of mouse and human shows an infralow-oscillation (ISO, ~50-s period) in the spindle power band (sigma, 10–15 Hz) that generates alternating states of high and low arousability, which is phase-locked to variations in heart rate and pupil diameter. The neural circuits underlying the ISO are currently unknown. A candidate nucleus is the locus coeruleus (LC), which is key for arousal and attention during wakefulness, but that remains active during NREMS and controls sleep spindle generation and sensory arousability.

Methods: We studied projections from noradrenergic LC neurons to the dorsal and reticular thalamic nuclei through the retrograde viral labeling of dopamine- β -hydroxylase (DBH)-expressing neurons in 7 to 10-week-old C57Bl/6J mice. To assess their role in NREMS, we inhibited α -adrenergic and β -adrenergic receptors through the local infusion of atenolol (5 mM) and prazosin hydrochloride (0.1 mM) into primary thalamic somatosensory areas, and recorded pre-injection and post-injection sleep–wake behaviour from ZT1–7 in freely moving animals implanted with ipsilateral somatosensory (S1) local field potential electrodes together with polysomnography ($n = 5$).

Results: Anatomical projections from LC to the thalamus arise from densely packed subgroups of DBH-expressing neurons in the anterior half of the LC. Compared to the baseline, the pharmacological inhibition of thalamic adrenergic receptors reduced the power of the oscillatory sigma pattern in

NREMS in the ~50-s range (from 0.12 ± 0.06 nV2 to 0.04 ± 0.02 nV2) and suppressed the phase relation of discrete spindles to the ISO (r of Rayleigh from 0.57 ± 0.05 to 0.30 ± 0.06). Moreover, the absolute sigma activity in S1 during the phases of low sigma power of ISO was increased (from 0.31 ± 0.08 a.u. to 0.42 ± 0.12 a.u.).

Conclusions: We identify the anatomical and functional relation between the LC and the reticular and dorsal thalamus during NREMS, and propose that the phasic release of noradrenaline into thalamic sleep spindle-generating circuits as part of the circuitry underlying the mammalian ISO.

Funding: This project is funded by an international PhD Fellowship of UNIL-FBM and by SNF.

6. Prediction of Sleep Apnea Severity Using A Portable Electrocardiogram Monitoring Device

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Background: Sleep apnea syndrome (SAS) is diagnosed and graded by polysomnography (PSG) based on the number of apnea–hypopnea events per hour of sleep (apnea–hypopnea index, AHI). PSG is expensive and technically complex; therefore, simpler and more cost-effective devices for screening and follow-up are desirable. In this context, a wearable electrocardiogram (ECG) acquisition system was developed by the Swiss Federal Laboratories for Materials Science and Technology (Empa). The aim of the present study was to evaluate the value of overnight ECG recordings to assess apnea severity using an ECG belt in a population of patients with suspicion of SAS.

Methods: The ECG belt consists of a semi-elastic polyester backbone with directly embroidered Ag/Ti-coated PET yarn forming the electrodes. Patients with suspicion of SAS were recruited. An ECG signal was recorded in every patient using both the belt and PSG. Heart rate variability (HRV) analysis was carried out, and a prediction model using support vector machine was applied. The prediction accuracy of apnea severity was assessed for both signal acquisition systems.

Results: Whole night measurements were performed on 241 patients. The median AHI was 21 [IQR: 7–40]/h and 65% of the patients suffered from SAS (AHI >10/h). The ECG belt had an accuracy, sensitivity, and specificity of 72%, 70%, and 74%, respectively, to discriminate individuals without SAS and individuals with SAS of different degrees of severity, which was comparable to PSG. The prediction accuracy was comparable to PSG and particularly suitable for the discrimination between patients with no/mild SAS versus moderate/severe SAS.

Conclusions: In individuals suspected of SAS, a novel textile-based ECG belt was able to detect HRV-based disturbances of the vegetative nervous system, which allowed for the assessment of sleep apnea severity. The follow-up of patients with SAS could be complemented by HRV, giving additional insights into the cardiovascular stress level during sleep.

Funding: The study was supported by an unconditional research grant by the Lungenliga St. Gallen—Appenzell and an institutional grant by the Kantonsspital St. Gallen.

7. Overnight Changes in EEG Slow Wave Slopes in the Course of Development

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Background: The restorative function of sleep has been linked to an overall reduction in synaptic strength. The synaptic homeostasis hypothesis proposes that synaptic renormalization during sleep occurs in a “smart” manner: while most synapses are selected for renormalization, some synapses are protected from down-selection. During brain development, major synaptic restructuring occurs, and impairments in synaptic down-selection during sleep may be associated with cognitive and memory deficits in clinical populations. Synaptic down-selection has been connected to slow waves during non-rapid eye movement (NREM) sleep. While both the amplitude and the slope of slow waves decrease during sleep, the slope is thought to most directly reflect synaptic strength, when controlling for amplitude changes across the night. Here, we aimed to examine overnight slope changes in the course of development in a region-dependent and amplitude-dependent manner.

Methods: All-night high-density electroencephalogram (EEG) was recorded in 60 healthy subjects aged between 8–30 years (mean \pm s.e.m., 18.9 ± 0.8 years, 25 females). To control for amplitude changes across the night, we matched slow waves from the first and the last hour of NREM sleep according to their amplitude.

Results: Our results show that slow wave slopes decreased from the first to the last hour of NREM sleep ($F_{\text{time}}(1,58) = 289.6, p < 0.001$) across the cortex. This global overnight slope reduction was largest in children and decreased with age ($r = -0.510, p < 0.001$). Topographical analyses revealed regional differences in the slow wave slope decrease, which were dependent on amplitude. Specifically, for small amplitude waves, the decrease was smallest over an occipital area, whereas for large amplitude waves, the decrease was smallest over a central area ($F_{\text{occipital}}(7,392) = 4.81, p < 0.001, F_{\text{central}}(7,392) = 8.75, p < 0.001$).

Conclusions: The larger slope decrease in children suggests a boosted down-selection of synapses during sleep in childhood, which in turn might be related to increased plasticity during brain maturation. Regional differences in the extent of slow wave slope reduction may reflect the “smart” down-selection process or, alternatively, indicate amplitude dependent differences in the generation of slow waves. These results reveal the need to consider age when using the overnight slope change as a biomarker in clinical populations.

Funding: SNF Sinergia CRSII3_160803, CRPP “Sleep and Health”, SNF 320030_153387

8. New Learning during Sleep

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9. Diurnal Changes in Cortical Glutamate + Glutamine Levels from Childhood to Adulthood and their Relationship to Sleep

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Background: Sleep slow waves play a crucial role in maintaining cortical plasticity, which is a process that is especially important in the developing brain. Children show a considerably larger overnight decrease in slow-wave activity (SWA; EEG power between 1–4.5 Hz), which constitutes the primary

EEG marker for the restorative function of sleep. In healthy young adults, we recently demonstrated that this EEG marker correlates with the overnight reduction in cortical glutamate + glutamine (GLX) levels assessed by magnetic resonance spectroscopy (MRS), suggesting GLX as a promising biomarker for the interplay between cortical plasticity and SWA. Since brain maturation depicts a time window of increased cortical plasticity and increased sleep need, we examined age-related overnight changes in GLX and SWA from childhood to adulthood.

Methods: The MRS spectra of 46 subjects (mean \pm s.e.m., 16.5 ± 0.78 years, 24 females) were measured in the left parietal lobe in the evening before a night of sleep and in the subsequent morning using a 3T GE MR 750 scanner. GLX concentrations were quantified using a locus coeruleus (LC) model and corrected for a partial volume contamination of cerebrospinal fluid (CSF). The decrease of SWA in the course of the night was calculated as a percentage reduction from the sleep cycle with maximal SWA to the last sleep cycle.

Results: The overnight changes in GLX correlated negatively with age ($p = 0.01$, $r = -0.4$), differed between children (<12 years) and adults (>18 years; $p < 0.05$; pairwise comparisons using a Mann–Whitney U-Test, *fdr* adjusted) and changed its sign from positive to negative (mean children = 6.3%, mean adults = -5.4%). No other metabolites showed a significant correlation for overnight changes with age (all $p > 0.2$). We found no correlation between changes in GLX and (a) the reduction in SWA ($p = 0.4$), (b) the duration of wake after sleep onset, or ($p = 0.4$) (c) the duration of REM sleep ($p = 0.6$).

Conclusions: Given that children and adolescents show a higher decline in SWA over the course of the night, we expected that GLX reductions would be more pronounced within this cohort. Here, we find the contrary: namely, a more pronounced overnight decrease in adults compared to children. If reorganizational processes during brain development might mask diurnal changes in GLX levels or if these manifest after cortical maturation is completed needs to be elucidated in the future.

Funding: Swiss National Science Foundation (320030_153387) and the Clinical Research Priority Program (CRPP) Sleep and Health of the University of Zurich.

10. Evening Caffeine Intake Induces Alertness in Teenagers, but Does Not Affect Melatonin Levels

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Background: Adolescents suffer from short sleep duration and frequently consume caffeine in the evening. Observational studies indicate worse academic performance and lower quality of sleep in teenagers reporting frequent caffeine consumption. However, so far, caffeine-induced changes in sleepiness, performance, and sleep quality in teenagers have not been systematically investigated.

Methods: In a placebo-controlled double-blind within-subject laboratory study, 18 teenagers (15.6 ± 1 years old, self-reported habitual caffeine intake: 241 ± 123 mg/week) ingested 80 mg of caffeine (versus placebo) four hours prior to habitual bedtime after one week of caffeine abstinence. Until bedtime and over 1.5 h after waking up, participants regularly filled in the Karolinska Sleepiness Scale and performed in a psychomotor vigilance and an N-back task (with varying working memory load: 2-back versus 0-back). Subjective sleep quality was measured in the morning by the Leeds

Sleep Evaluation Questionnaire. Saliva samples were taken regularly under dim light conditions to determine caffeine and melatonin levels.

Results: After intake, caffeine levels increased until bedtime and did not fully return to baseline levels in the morning ($p < 0.01$). Subjective sleepiness was lower, median reaction times were faster, and the number of attentional lapses ($RT > 500$ ms) reduced ($p < 0.05$) after caffeine compared to placebo. In the N-back task, independent of load, a plateau of high performance (correct responses) was reached faster after caffeine compared to placebo (interaction condition * time $p < 0.05$). Finally, the participants indicated a worse quality of falling asleep after caffeine compared to placebo ($p = 0.05$), while no treatment-induced differences were observed in salivary melatonin levels ($p > 0.1$).

Conclusions: The data suggest that caffeine intake in the evening (in a dose equivalent to 250 mL of common energy drinks) induces arousal in teenagers, and is mirrored in lower sleepiness and higher attentional performance. While caffeine did not induce a circadian phase delay in the present sample, the worse quality of falling asleep still suggests that a caffeine dose of 80 mg in the evening can be sufficient to contribute to teenagers' shortened sleep durations, as frequently observed during schooldays.

Funding: Swiss National Science Foundation PMPDP1_171364 / 1

11. Changes in Cross-Frequency Coupling Following Closed-Loop Auditory Stimulation during NREM Sleep

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Background: Phase-amplitude coupling between the neocortical slow waves (SW) and faster oscillations is thought to facilitate the coordinated information processing in the multiple brain areas that are necessary for sleep-dependent memory consolidation. Recently, it was demonstrated that by targeting SWs in a particular region with closed-loop auditory stimulation, it is possible to locally manipulate SW activity and interact with ongoing training-induced neuroplastic changes [1]. Capitalizing on this finding, we tested whether closed-loop auditory stimulation might locally affect coupling between SW and power in theta and sigma bands.

Methods: For this, we recorded high-density sleep EEG in nine subjects (23 ± 1.3 years old) under two conditions: (1) non-stimulation (SHAM) and (2) closed-loop auditory stimulation (STIM) targeting the up-phase of real-time detected SW in electrode C4 (target electrode). We calculated the modulation index [2], reflecting the association between phases in the 0.75 Hz to 2.75 Hz (SW) range and power in the 4–30 Hz band.

Results: In the STIM condition, there was a significant decrease of SW–theta coupling by $31 \pm 18\%$ in the frontal channels ($p = 0.02$, $d = -1.64$), which was the area of the strongest default coupling both in STIM and SHAM conditions. In contrast, a significant increase by $124 \pm 105\%$ in SW–sigma coupling was observed over the right parietal area, which was located directly posterior to the target electrode ($p = 0.01$, $d = 1.15$).

Conclusions: Here, we present initial evidence that closed-loop auditory stimulation locally modulates coupling between SW and sigma in a target region. This opens the way to a variety of future implementations of closed-loop auditory stimulation in different populations with local pathology-related changes in cross-frequency coupling, such as in the case of medial frontal atrophy in older adults [3].

Funding: This study was supported by the Swiss Government Excellence Scholarship (Elena Krugliakova), by the Clinical Research Priority Program (CRPP) "Sleep and Health", the HMZ flagship grant SleepLoop and the SNF Foundation grant 320030_153387 (Reto Huber).

12. Fear Learning, Slow-Wave Sleep, and Trait Anxiety: A Conditioning Study

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Background: Fear conditioning is widely used as a model of fear learning, informing our understanding of post-traumatic stress disorder and other related pathologies. Fear learning has been strongly related to sleep disruption and trait anxiety, however these factors have largely been studied independently. We used a fear conditioning, extinction, and reinstatement design to investigate how sleep and anxiety are associated with fear learning.

Methods: Healthy participants ($N = 20$, 18 females, aged 19–28) underwent a two-day fear conditioning paradigm. On day 1, participants were successfully conditioned to fear (CS+) and safe (CS-) stimuli, where CS+ trials were paired with an aversive electric shock (56% reinforcement). Then, overnight sleep at home was monitored with wearable electroencephalography (EEG). On day 2, participants underwent extinction, reinstatement, and re-extinction. Skin conductance response (SCR) was used to measure fear during conditioning and extinction phases.

Results: Strength of fear conditioning was associated with subsequent sleep, with better learned CS+/CS- discrimination associated with a lower percentage of slow-wave sleep (SWS%) at a trend level, $p = 0.054$. Overnight consolidation of discrimination was then significantly positively correlated with SWS%, $p = 0.050$. Finally, trait anxiety predicted reinstatement effects. Prospective anxiety was associated with lower CS discrimination after reinstatement, $p = 0.016$, and inhibitory anxiety was associated with a lack of extinction, shown by greater fear responses to both the CS+, $p = 0.009$ and CS-, $p = 0.007$ at the end of re-extinction.

Conclusions: Current literature suggests that fear conditioning as a stressful experience impacts subsequent sleep. Here, our findings suggest that the strength of learning may affect the proportion of subsequent sleep dedicated to SWS, and in turn, this SWS supports the consolidation of the distinction between safe and fear stimuli. Furthermore, we show that trait anxiety predicts return of fear, and a failure to subsequently extinguish fear responses after reinstatement despite no further fear learning. These data highlight the importance of SWS in fear learning and trait anxiety in return of fear. This could support future work investigating sleep manipulation during SWS to attenuate learned fear.

Funding: No funding.

13. Increased Neuronal Signatures of Targeted Memory Reactivation during Slow-Wave Up-States

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Background: It is assumed that the memory function of sleep relies on the spontaneous reactivation of newly acquired memories. Those spontaneous reactivation processes are driven by the cortical slow oscillations, while inducing memory reactivations by re-exposure to learning-associated memory cues (TMR) results in enhanced memory performance. Slow oscillations consist of alternating phases of periods of increased neural firing (up-state) and widespread neural silence (down-state), which roughly corresponds to the positive half wave and negative half wave of the surface slow wave (SW). As the

benefits of TMR during sleep might depend on periods of increased neural firing, we hypothesised that cueing foreign vocabularies during SW up-states would lead to enhanced recall performance as compared to words presented during down-states or uncued words, speaking for the crucial role of SW up-states in the reactivation of memories.

Methods: Native German speakers learned 120 Dutch–German word pairs in the evening. During subsequent non-rapid eye movement (NREM) sleep, slow waves (SWs) were detected online. One-third of the prior learned Dutch words were repeatedly presented during SW up-states, one-third during down-states, and one-third were not presented at all. Average word length was 500 ms, to fit in either an SW up-state or down-state. After three hours of nighttime sleep, the word knowledge was tested using a cued recall procedure.

Results: Words replayed during SW up-states benefited the most as compared to uncued words. Still, down-state replayed words benefited as well, but to a lesser degree than the up-state replayed words. On average, words replayed in an SW up-state were played at 345° of the slow-wave, whereas down-state words were replayed at 130°.

Conclusions: Replaying words during the SW up-state phase is related with the strongest memory enhancing effects, suggesting that TMR is more likely to be processed and enhance memory when the stimuli are played during a SW up-state. These findings show that memory enhancement by reactivation during an SW up-state is more stable, but is more variable when the reactivation occurs outside of the up-state. Future analyses will aim for characterising what makes cueing the most beneficial.

14. Daily Caffeine Consumption Reduces Human Grey Matter in Hippocampus Independent of Sleep Pressure

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Background: Acute caffeine consumption alters sleep–wake regulation by dampening the accumulation of sleep pressure, which is indexed by the reduction in electroencephalographically (EEG)-derived slow wave activity (SWA) during sleep. High sleep pressure has been found to result in reduced grey matter (GM). Therefore, we were interested in whether daily caffeine consumption affects GM, and whether these changes are mediated by sleep pressure.

Methods: Twenty male habitual caffeine consumers (aged 26.2 ± 4.1 years, average daily caffeine consumption 471.5 ± 112.24 mg) completed a double-blind randomized study. Each volunteer received both caffeine (3×150 mg/day) and placebo for 10 days. After nine days, EEG-derived SWA was measured during nighttime sleep. On day 10, GM was measured via T1-weighted Magnetization-Prepared Rapid Acquisition with Gradient Echo (MPRAGE) in a 3T MRI scanner. The scan took place after 12.5 h of EEG-controlled wakefulness in constant posture and a dim light environment. Differences in total and regional GM between conditions were estimated first. In the next step, we adjusted for SWA (during the first NREM cycle) and cerebral blood flow (CBF) measured

by 2D EPI Arterial Spin Labeling (ASL) to test the mediation of sleep pressure on GM and to control for CBF influence on blood-oxygen-dependent-level (BOLD) signals.

Results: In the caffeine condition, total GM was lower compared to placebo ($p = 0.040$). Voxel-wise analyses indicated that the most prominent GM decrease in caffeine compared to placebo was in the hippocampus ($p_{\text{FWE}} = 0.032$), along with the left frontal pole, postcentral gyrus, right insula, and the cerebellum at trend (i.e., $p_{\text{FWE}} < 0.062$, $p_{\text{FDR}} = 0.029$.) SWA did not differ between conditions, and correcting for SWA did not affect the coefficient of condition on GM. However, after correcting for total CBF, total GM reduction was no longer significant ($p = 0.522$), while the reduction in hippocampal GM remained significant ($p_{\text{FWE}} < 0.05$) after adjusting for regional CBF.

Conclusions: Our data indicate that hippocampal GM reduces in response to daily caffeine consumption. Despite earlier evidence that hippocampal neurogenesis is sensitive to high sleep pressure, the SWA in the previous night's sleep did not explain the observed hippocampal caffeine-associated GM reduction. It remains to be clarified whether the reduction results from the neuroinflammatory apoptosis or neuroexcitotoxicity via the chronic blockade of adenosine.

Funding: Swiss National Science Foundation (320030- 163058).

15. The Effects of Repeated Daytime Caffeine Intake and Its Cessation on Nighttime Sleep

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Background: Acute caffeine intake, particularly in the evening, has repeatedly been associated with signs of disturbed sleep such as prolonged sleep latency, reduced sleep duration, decreased EEG delta, and increased sigma power density during non-rapid eye movement (NREM) sleep. However, the effects of repeated caffeine consumption during morning and/or afternoon hours, which is an intake pattern that is prevalent in about 80% of caffeine consumers, remain unknown.

Methods: Twenty male healthy regular caffeine consumers (26.4 ± 4.0 years old, habitual daily caffeine intake 474.1 ± 107.5 mg) completed a double-blind, within-subjects study including a caffeine (3×150 mg caffeine for nine days), a placebo ($3 \times$ placebo for nine days), and a withdrawal condition (3×150 mg caffeine for eight days followed by a change to placebo on day nine). After nine days of continuous treatment, EEG-derived sleep structure and intensity were recorded during 8 h of nighttime sleep, beginning 8 h and 15 h after the last caffeine pill in the caffeine and withdrawal condition, respectively. Subjective sleep quality was measured by the Leeds Sleep Evaluation Questionnaire (LSEQ).

Results: Sleep latency, total sleep time, and the duration of sleep stages did not significantly differ between conditions ($p > 0.2$). However, the all-night spectral power density in the sigma band (12–16 Hz) during NREM sleep was significantly reduced in both the caffeine and withdrawal condition compared to placebo ($p < 0.05$). Subjective sleep quality did not significantly differ between conditions ($p > 0.1$).

Conclusions: Our data indicate that daily caffeine consumption does not lead to clear-cut changes in nighttime sleep structure, when assessed 8 h and 15 h after the last intake. Similarly, subjective sleep quality was not significantly affected by the treatment. However, NREM sleep power density in the

sigma range seems to be a sensitive marker mirroring caffeine-induced changes under conditions of daily intake. Its decrease during daily caffeine intake is at first glance in contrast with the increases reported after acute caffeine treatment in earlier studies. However, it can be reconciled within the assumption of a daily overnight withdrawal from the substance.

Funding: This work was supported by the Swiss National Science Foundation (320030_163058), the Nikolaus und Bertha Burckhardt-Bürgin-Stiftung, and the Janggen-Pöhn-Stiftung.

16. The Influence of Pre-Sleep Social Media Consumption and Relaxation on Sleep Quality

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Background: Due to the current trend to digitalization, it is important to examine effects of the use of respective media channels on different aspects in individuals' lives. Besides the potential of this trend, digitalization may also have negative effects, as it might reinforce societal gaps through creating a digital divide, foster excessive media use, or decrease trust in media and impair political participation. A recurring question revolves around the negative impact of media use on sleep quality. Sleep is considered to be important for different body functions such as the reconstitution of energy, facilitation of the immune system, and memory consolidation. Intensive media use can lead to a state of cognitive hyperarousal, which has been recently shown for the use of electronic media, smartphones, as well as social media. As cognitive hyperarousal has been reported to negatively affect sleep, we hypothesize that intensive social media use before sleep will negatively affect objective and subjective sleep quality.

Methods: To investigate the influence of social media use on sleep quality, a one-factorial experimental study was conducted. Thirty young and healthy participants spent four nights in a sleep lab. Within experimental conditions, participants either used social media for 30 min before sleep (while wearing blue light-blocking glasses) or followed instructions of a progressive muscle relaxation training for 30 min, or slept directly. In order to get objective sleep parameters, sleep was recorded by polysomnography (EEG, EMG, EOC, ECG, and respiration). Participants rated their subjective sleep quality in the morning.

Results: Initial analyses of sleep data show that 30 min of social media use before bedtime impacts sleep architecture: Social media use before sleep reduced the proportion of time participants spent in sleep stage N2, whereas it prolonged the time spent in N1. Further sleep onset latency was reduced after 30 min of relaxation training.

Conclusions: Our results sustain the notion that neither relaxation nor social media use immediately before sleep have a strong effect on sleep and sleep-associated functions: sleep latency was reduced after relaxation, whereas N1 was prolonged after social media use. Further analyses will include the comparison between different subgroups of participants in this experiment, e.g., by dividing the group with respect to their intensity of social media use (low versus high).

Funding: ERC Starting Grant: MemoSleep 677875.

17. Phase-Coupled Sleep Oscillations within and between Human Hippocampus and Neocortex

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Background: New memories undergo a gradual transfer from the hippocampus (HPC) to the neocortex (NC), with this memory consolidation process preferentially taking place during sleep. Precisely timed neural oscillations interacting within and between these brain structures are thought to mediate this sleep-dependent memory reorganization. However, which components of the large constellation of sleep oscillations instantiate this HPC–NC dialog in the human brain, and via what mechanisms, remains elusive.

Methods: We recorded invasive electroencephalography from the HPC and lateral temporal cortex in 10 neurosurgical patients during stages N2 and N3 of non-rapid eye movement sleep, as well as rapid eye movement (REM) sleep.

Results: We identified several forms of HPC–NC communication, belonging to two broad classes of interregional oscillatory coordination. First, we observed interregional phase synchrony in the sleep spindle (N3) and theta (N2, REM) frequency bands. Second, we found cross-frequency coupling between the phase of HPC slow oscillations and the amplitude of NC activity spanning the delta, theta, beta, gamma, and ripple ranges (N3).

Conclusions: These previously unknown HPC–NC communication lines add to our understanding of the oscillatory organization of the sleeping brain, and may offer a physiological basis for the sleep-dependent reorganization of mnemonic content.

Funding: This work was supported by the German Research Foundation (FE366/9-1 to JF) and a Wellcome Trust/Royal Society Sir Henry Dale Fellowship (107672/Z/15/Z to BPS).

Clinical Science

18. REM-Sleep Related Heart Rate Variability Distinguishes between Insomnia and Normal Sleep

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Background: In insomnia disorder, a mismatch between a subjective perception of poor sleep and quite normal objective sleep EEG results is a common finding. The aim of this study was to evaluate the capability of sleep stage-related heart rate variability (HRV), which is a correlate of autonomous nervous system activity, to objectify insomnia.

Methods: 47 adults (age: 39.7 ± 12.5 years, 51.1% females) suffering from primary insomnia according to DSM-IV criteria were compared to a control group of 23 adults (age: 37.6 ± 12.3 years, 60.9% females) with no sleep complaints. Sleep was objectively assessed with polysomnography. HRV was assessed in artefact-free five-minute ECG segments of pure sleep stages. Sleep EEG variables and sleep stage-related HRV frequency domain measures, such as the power of high frequency (HF), low frequency (LF), and very low frequency (VLF) bands, were compared between patients and controls.

Results: Insomnia and normal sleep did not differ in regard to any of the common measures of objective sleep continuity and sleep architecture, except for a lower amount of REM sleep (%) in insomnia. In the insomnia group, the absolute HRV frequency power over all the frequency bands was suppressed in REM sleep and NREM sleep. Furthermore, in the first available REM sleep ECG segments, the relative HF power was decreased, and the relative VLF power was increased (with large effect sizes, respectively).

Conclusions: These results are in line with the theory of hyperarousal in insomnia. Sleep stage-related HRV analysis and specifically HRV in early REM sleep deliver more sensitive biomarkers for insomnia than common sleep EEG variables. Furthermore, REM sleep-related HRV might be a proxy for central autonomous network activity.

Funding: No funding.

19. Sleep Determinants of Incident Cardiovascular Events: A Prospective Population-Based Study

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Background: This study aimed to assess the sleep determinants of incident cardiovascular events in a general population sample.

Methods: HypnoLaus is a prospective middle-to-older-age population-based cohort in which 2162 participants underwent a complete polysomnography at home, answered sleep questionnaires, as well as had their cardiovascular (CV) profile assessed at baseline and at a five-year follow-up. A local committee adjudicated the development of any CV event (myocardial infarction, acute coronary syndromes, or stroke) following international recommendations. The apnea-hypopnea index (AHI) ≥ 15 events/h defined obstructive sleep apnea (OSA). A Pittsburgh Sleep Quality Index (PSQI) score > 5 defined poor sleep quality. The fast Fourier transformation of non-rapid eye movement (NREM) electroencephalogram (EEG) assessed relative power spectrum components. Autonomic activation during sleep was evaluated through pulse wave amplitude (PWA) drops based on the photoplethysmographic signal of pulse oximetry. Multivariable-adjusted COX regressions were used for statistical analysis.

Results: Of the 1939 participants (56.4 ± 17.7 years, 53.0% women) free of any CV event at baseline, 74 (3.8%) developed a CV event over a five-year follow-up. After adjustment for age, sex, body mass index, systolic blood pressure, smoking, alcohol, metabolic syndrome, dyslipidemia, and hypertension, the following sleep parameters were independently associated with the development of incident CV events: PWA drop index (hazard ratio, HR, for one event/h increase: 0.986 [0.974–0.999], $p = 0.033$), NREM delta EEG power (HR for 1% increase: 0.951 [0.918–0.985], $p = 0.005$), and PSQI > 5 (HR vs. PSQI ≤ 5 : 2.275 [1.342–3.855], $p = 0.002$). OSA and hypoxia-related sleep parameters were not significantly associated.

Conclusions: Impaired vascular reactivity assessed by PWA variations, low NREM delta power, and subjective poor sleep quality are independent predictors of incident CV events in the HypnoLaus cohort.

Support: Leenaards foundation, FBM, and SNF.

20. Circadian Modulation of Core Body Temperature in Patients with Central Hypersomnia Disorders

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Background: An intact and regular sleep–wake rhythm is the basis for a healthy life. This is ensured by the circadian pacemaker, which drives the sleep–wake cycle to maintain stable vigilance during the day and consolidated sleep during the night. In patients with central hypersomnia, these day–night differences seem less pronounced. However, the knowledge about the interplay between the circadian and the homeostatic sleep–wake regulation in these diseases is limited.

Methods: Core body temperature (CBT) has been shown to be a distinct marker of the circadian rhythm. Here, we studied the circadian modulation of CBT over a 24-h day. After a baseline night, a constant condition protocol (controlled room temperature, light <10 lux, low activity (sitting/lying in a bed), isocaloric and temperature-controlled meals) was performed over 40 h. Ten naps of 80-min sleep opportunity were scheduled in equal intervals to control for homeostatic sleep pressure. CBT was continuously measured with a wireless ingestible core body temperature sensor (HQ Inc., Florida). The modulation of CBT was analysed with a cosinor regression (period of 24 h) over the sleep episodes. We present the preliminary results of six unmediated patients with narcolepsy type 1 (Nt1), six patients with idiopathic hypersomnia (IH), and six healthy controls (HC).

Results: The results show a clear CBT modulation in all the patient groups. IH showed an increased mean temperature (IH/Nt1/HC: 37.2 °C/37.08 °C/37.08 °C), a higher modulation amplitude (IH/Nt1/HC: 0.24 °C/0.21 °C/0.2 °C) and a shorter acrophase (IH/Nt1/HC: 9.11 h/8.85 h/9.89 h), implying an earlier peak temperature with respect to the subject-specific bedtimes than the control group. No significant group differences were found.

Conclusions: This protocol allowed isolating the circadian modulation of core body temperature regulation from external conditions. The results indicate that the circadian rhythm of thermoregulation is maintained even in patients with central hypersomnia disorders. However, these results are based on preliminary data, and other markers than CBT might still reveal a change in circadian pattern.

Funding: This research is funded by the swiss national research foundation.

21. Behavioural and Regional EEG Features of Parasomnia Episodes in Disorders of Arousal

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Background and Aims: Disorders of arousal (DoA) are NREM parasomnias that are characterised by incomplete awakenings from slow-wave sleep (SWS) and abnormal behaviour. Previous work showed that parasomnia episodes (PE) display features of both sleep and wake in different brain areas. However, these observations are based on single episodes, and it is unclear how dissociated patterns of sleep and wakefulness relate to behaviour. Here, we investigated how behaviour and brain activity measured with high-density (hd) EEG differed between PE and normal awakenings (NA) in healthy controls (HC) and DoA patients.

Methods: 18 patients with DoA (13F, age 26.4 ± 5.3) underwent a baseline and a second hd-EEG sleep recording coupled with acoustic stimulations after 24 h of total sleep deprivation. Fourteen HC (10F, age 26.5 ± 4.7) underwent a baseline hd EEG recording. Video recordings of all awakenings from SWS were inspected and rated as NA or PE by three independent expert scorers. After a thorough artifact removal procedure, topographical spectral power (2–35 Hz) and behavioural features were compared using paired nonparametric statistics with correction for multiple comparisons and chi square tests, respectively.

Results: Compared to awakenings rated as NA ($n = 47$), those rated as PE ($n = 80$) were associated with eye opening, a more rapid onset, a reorienting reaction, perplexity, somniloquia, fear, hallucinations, and environmental interactions ($p < 0.001$ for all, except for fear, $p < 0.05$). Compared to NA in DoA patients, PE were associated with significantly lower sigma (12–16 Hz) and alpha power (8–12 Hz)

in posterolateral brain regions ($p < 0.05$, $n = 11$) and marginally increased delta power (2–4 Hz) in central posterior areas. Compared to NA in HC, NA in DoA patients displayed diffusely decreased beta power (18–30 Hz) peaking in frontal brain regions ($p < 0.05$, $n = 7$).

Conclusions: Behavioural features that distinguish PE from NA include eye opening, a more rapid onset, a reorienting reaction, perplexity, somniloquia, fear, hallucinations, and interactions with the environment. Spectral analysis suggests that an “incomplete awakening” of posterior brain regions appears to characterise PE. Further analyses will establish how these differential brain activity patterns relate to behaviour and conscious experiences.

Funding: SNSF Grant PZ00P3_173955; Théore-Ott Grant.

22. Nocturnal Gamma-Hydroxybutyrate (GHB) Reduces Cortisol Awakening Response and Morning Tryptophan Catabolites in Healthy Volunteers

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Background: Gamma-hydroxybutyrate (GHB) is an endogenous GHB-/GABAB receptor agonist that has been approved for the treatment of narcolepsy and proposed for the potential treatment of various neuroimmunological diseases, including Alzheimer’s disease, Parkinson’s disease, fibromyalgia, and depression. Tryptophan catabolites (TRYCATs), the cortisol-awakening response (CAR), and brain-derived neurotrophic factor (BDNF) have all been suggested as peripheral markers of neuroimmunological processes. In addition, GHB was shown to induce a delayed reduction of T helper and natural killer cell counts and alter basal cortisol levels. By contrast, GHB’s effects on TRYCATs, CAR, and BDNF are unknown.

Methods: TRYCATs and BDNF plasma levels, CAR, as well as affective state (Positive and Negative Affect Schedule, PANAS) were measured in the morning after a single nocturnal dose of GHB (50 mg/Kg body weight), which was administered at 02:30 to 20 healthy male volunteers. A placebo-controlled, balanced, randomised, double-blind, cross-over design was used.

Results: Following GHB, the TRYCATs, indolelactic acid, kynurenine, kynurenic acid, 3-hydroxykynurenine, quinolinic acid, the 3-hydroxykynurenine to kynurenic acid ratio, and CAR were significantly reduced when compared to placebo ($p < 0.05$ – 0.001 , Benjamini–Hochberg corrected). The quinolinic acid to kynurenic acid ratio was reduced by trend. Serotonin, tryptophan, and BDNF levels, as well as PANAS scores, were unchanged after nocturnal GHB challenge.

Conclusions: It is concluded that GHB post-acutely affects peripheral markers of neuroimmunological processes. The GHB-induced changes may serve as a model to explain some of GHB’s therapeutic effects in neuropsychiatric disorders involving neuroimmunological pathologies.

Funding: No funding.

23. Feeling Awake during Sleep: A High-Density EEG Assessment of Sleep Perception in Good Sleepers and Patients with Paradoxical Insomnia

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Background: The impression of being awake despite polysomnographically documented sleep is sometimes reported by healthy individuals (good sleepers control, GSC) and to an extreme degree by patients with paradoxical insomnia (ParI). The mechanisms underlying the subjective perception of sleep are not well understood. Here, we asked whether high-density (hd) EEG, a technique with a refined spatial resolution, could identify local patterns of brain activity related to the subjective perception of sleep in ParI and GSC subjects.

Methods: Nine ParI (41.54 ± 6.50 (SD)) and 9 GSC (40.61 ± 6.82 , age-sex matched, 7F), equipped with hd EEG (256 channels), underwent a baseline and two experimental sleep recordings combined with a serial awakening paradigm. At each awakening, they were asked whether they had felt asleep (FAS) or awake (FAW) immediately prior to the awakening.

Results: ParI patients strongly underestimated their total sleep time ($p = 2.88 \times 10^{-4}$) and overestimated their wake after sleep onset time ($p = 0.0019$). As expected, in experimental nights, FAW instances occurred more often in ParI than in GSC ($p = 0.0044$ for N2 and N3 combined). In both groups, they appear to cluster early in the night ($p = 0.0138$), and tended to be associated with more thought-like and less perceptual conscious experiences compared to FAS ($p = 0.0642$). In GSC, FAWs instances were preceded by short-lasting increases in gamma power (30–45 Hz) in the vertex region, while in ParI patients, FAWs were associated with more diffuse and longer-lasting power increases in a broader frequency range (10 Hz to 45 Hz).

Conclusions: We show that the subjective impression of feeling awake during sleep is associated with objective EEG changes (high-frequency power increases), which are rare, short-lasting, and localised in healthy subjects and more frequent, long-lasting and diffuse in patients with paradoxical insomnia. The spatio-spectral characteristics of these changes suggest that feeling awake may result from differential degrees of arousal system activations in the two populations. In light of these results, ParI patients seem to correctly perceive localized “wake-like intrusions”, rather than misperceive their sleep as commonly assumed.

Funding: SNSF Grant PZ00P3_173955; Théodore-Ott Grant

24. “Sleep Well, My Dear, to Be Fit for Loving Motherhood”—Insomnia but not Objective Sleep Deficits Correlate with Poor Bonding

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Background: Insomnia has been acknowledged as a disorder of hyperarousal and impaired REM sleep stability, and there is accumulating evidence that insomnia is associated with disturbed stress coping and emotion regulation. As insomnia is a common complaint in postpartum mothers, the aim of this study was to examine whether subjective or objective maternal sleep quality has an impact on postpartum bonding. Our hypothesis was that insomnia was related to more parenting stress and delayed bonding. We further expected that this was due to a deficit in REM sleep in insomnia.

Methods: The sample consisted of 124 healthy mothers (mean age: 32.6 years) at three months after delivery. Subjective insomnia was assessed with the insomnia severity index (ISI), while in a sub-sample of 74 subjects, we also performed in-home sleep EEGs. We further assessed postpartum bonding, parenting stress, and depression.

Results: Maternal insomnia was correlated with delayed bonding, specifically increased “anxiety about care”; however, neither insomnia nor anxious bonding were associated with objective measures of sleep. There was a trend for decreased REM sleep in insomnia; however, a decreased amount of REM sleep did not mediate the relation between insomnia and anxious bonding. Moreover, insomnia was significantly related to postpartum depression and parenting stress.

Conclusions: In a sample of postpartum mothers, insomnia was related to more perceived stress, depression, and more anxious bonding, which support previous studies that related insomnia to negatively biased emotion processing. Moreover, interventions aiming at calming down hyperarousal in postpartum mothers may have implications for healthy bonding and child development.

Funding: Funding by an unrestricted grant from Gottfried and Julia Bangerter-Rhyner Foundation, Berne.

25. The Borderland Between Wakefulness and Sleep

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Background: The borderland between wakefulness and sleep is poorly defined. Yet, the scoring guidelines of the American Academy of Sleep Medicine (AASM) completely neglect it. We aimed to explore the borderland between wakefulness and sleep by focusing on microsleep episodes (MSEs) visible in the electroencephalogram (EEG) during the maintenance of wakefulness test (MWT). Such MSEs are of potential relevance for diagnosis and could have consequences while driving.

Methods: We retrospectively scored MWT trials of 76 randomly selected patients according to the AASM criteria and according to our own scoring criteria for MSEs. The MSE scoring was compared with quantitative EEG analysis.

Results: The quantitative EEG analysis enabled a reliable objectification of the visually scored MSEs. The latency to the first MSE was significantly shorter (mean: 15.18 ± 9.44 min) in comparison to the latency of sleep defined according to the AASM criteria (mean: 21.82 ± 11.63 min, $p < 0.0001$, $z = 5.645$). In certain cases, a large difference between the two latencies was observed (ranging from 0.05 to 33.85 min), and a great number of MSEs occurred between the first MSE and sleep (ranging from one to 31). Series of MSEs were more frequent in patients with shorter sleep latencies, while isolated MSEs were more frequent in patients who did not reach sleep.

Conclusions: The scoring of MSEs represents a valuable tool in addition to the AASM criteria, enabling an in-depth analysis of the borderland between wakefulness and sleep, which is particularly important in the maintenance of wakefulness test.

Funding: This work was supported by the Swiss National Science Foundation (grant 32003B_176323) and the Swiss Innovation Agency/Innosuisse (grant 17864.1 PFLS-LS).

26. Hypoxic Load and Subjective Daytime Sleepiness in the HypnoLaus Cohort

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Background: Although the Epworth Sleepiness Scale (ESS) is widely used to assess excessive daytime sleepiness (EDS) in clinical setting and research studies, its association with subjective and objective sleep parameters is still a matter of debate.

Methods: Data from 1982 participants (48.7% men, mean age 58.4 ± 11.1 years) of the population-based HypnoLaus study were analyzed. EDS was defined as an ESS score >10 . Ambulatory full polysomnography (PSG) as well as a clinical evaluation including medical history, lifestyle factors, and medication use were performed. Hypoxic load was calculated as the sum of the area under the curve of $\geq 3\%$ oxygen desaturations/total sleep time. The results were analyzed by multivariate generalised linear models (GLM) to assess means [95% confidence interval] adjusted for age, sex, body mass index (BMI), smoking status, alcohol, coffee consumption, and psychotropic drugs (benzodiazepines, hypnotics, and antidepressants).

Results: Compared to participants without EDS ($n = 1721$, 86.8%), participants with EDS ($n = 261$, 13.2%) had higher hypoxic load related to respiratory events during sleep (7.5 [5.5–10.2] versus 6.5 [4.9–8.7] % min/h; $p < 0.05$). A higher hypoxic load in the EDS group was also observed specifically during REM sleep (18.2 [13.2–25.1] versus 14.3 [10.6–19.3] % min/h; $p = 0.001$) as well as a higher percentage of sleep time with an oxygen saturation $<90\%$ (T90%: 6.7% [4.5–10.0] versus 5.1% [3.6–7.3]; $p = 0.01$). Other associations with EDS included objective and subjective sleep duration, which were lower in participants with EDS (TST: 402 [393–410] versus 415 [407–423] min; $p < 0.001$) as well as reduced relative delta power in N3 sleep stage (45.4% [43.8–47.1] versus 46.6% [45.1–48.2]; $p < 0.01$). By contrast, the arousal index, apnea-hypopnea index, and oxygen desaturation index did not differ between the two groups.

Conclusions: Hypoxic parameters such as hypoxic load and T90% are associated with higher EDS in our large middle-to-older age population-based sample.

Support: Leenaards Foundation, FBM, and SNF.

27. Epic Dreaming Disorder: Clinical, Polysomnographic and Dream Features in 12 Patients

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Background: Epic dreaming disorder (EDD) is a condition in which patients complain of excessive and relentless dreaming throughout the night that leaves them feeling tired the next day. Although regularly encountered in clinical practice, it is poorly documented, and no systematic assessment of dreaming has been performed in this population so far.

Methods: Here, we investigated the clinical characteristics of 12 EDD patients and 12 healthy gender-matched and age-matched controls (HC) through medical interviews and questionnaires. Seven EDD patients and 12 HC also underwent a baseline high-density EEG sleep recording, and six ED and eight HC completed one to two additional recordings combined with a serial awakening paradigm to inquire about dream experiences.

Results: EDD patients were predominantly middle-aged females (81.81%, mean age \pm SD: 35.36 ± 8.32). The disorder was lifelong in half of the patients and chronic in the remainder (mean duration 16.4 ± 8.44 years). EDD patients scored higher on anxiety and depression scales, and complained of lower sleep quality, as well as higher daytime sleepiness and fatigue. Sleep recordings revealed a higher microarousal index in EDD patients compared to HC ($22.74/h \pm 11.9$ versus $12.71/h \pm 5.11$, $p = 0.024$), but an otherwise preserved sleep architecture. The proportion of awakenings yielding dream reports was similar to control subjects ($74.38 \pm 21.91\%$ versus $89.25 \pm 13.76\%$, $p = 0.106$), but EDD patients presented significantly fewer dreams without recall of content in stage N2 ($23.7 \pm 29.11\%$ versus $56.73 \pm 18.52\%$, $p = 0.023$) and a trend toward a higher proportion of dreams with recalled content in rapid eye movement (REM) sleep ($92.06 \pm 13.69\%$ versus $59.22 \pm 40.81\%$, $p = 0.085$). Dream reports of EDD patients contained significantly more words overall and in REM sleep (overall: 49.57 ± 32.58 versus 17.29 ± 8.78 , $p = 0.014$, REM: 74.04 ± 44.27 versus 23.38 ± 8.8 , $p = 0.02$), and were rated as richer, more thought-like, and longer.

Conclusions: Our results do not sustain the hypothesis that EDD patients dream more than controls. Rather, they appear to recall the content of their dreams better in both REM and non-REM (NREM) sleep, and to display qualitative differences in dream characteristics. The increased microarousal index may explain why EDD subjects recall a higher number of dreams compared to control subjects.

Funding: FS is supported by a grant from Swiss National Science Foundation (PZ00P3_173955).

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