Accepted: 14 September 2022

DOI: 10.1111/jsr.13739

ABSTRACT

# Oral Abstract

## 1: PHARMACOLOGY AND BIOCHEMISTRY

### O002/P003 | Effects of clozapine-n-oxide and compound 21 on sleep in laboratory mice

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**Objectives/Introduction:** Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are chemogenetic tools for remote control of targeted cell populations using chemical actuators that bind to modified receptors. Despite the popularity of DREADDs in neuroscience and sleep research, potential effects of clozapine-N-oxide (CNO) and other DREADD actuators on sleep have never been systematically tested. Recent reports suggest that CNO can affect brain activity and animal behaviour, putatively through conversion to clozapine. The aim of our study was to assess whether CNO or compound 21 (C21), a novel actuator that cannot convert to clozapine, affect sleep in wild type laboratory mice.

**Methods:** We performed chronic electroencephalography (EEG) and electromyography (EMG) recordings in 16 male C57BL/6J mice housed under a 12/12 h light/dark cycle. Intraperitoneal injections of saline, CNO (doses: 1, 5, and 10 mg/kg; $n = 12, 16, 14$ mice), and C21 (dose: 3 mg/kg, $n = 7$ mice) were performed at light onset and sleep was analysed for 6 h following injections.

**Results:** Compared to saline, CNO injections led to a dose-dependent suppression of rapid eye-movement (REM) sleep ($F_{(2,\ 23)} = 7.525$, $p = 0.004$, Cohen's $d = -0.470$ [1 mg/kg], $-0.772$ [5 mg/kg], $-0.933$ [10 mg/kg]). CNO furthermore evoked changes in EEG spectral power during non-REM (NREM) sleep, and altered sleep architecture in a pattern previously reported for clozapine. C21 (3 mg/kg) also suppressed REM sleep ($t_{(6)} = 3.234$, $p = 0.009$, Cohen's$d = -1.222$), modulated NREM sleep EEG power spectra, and altered sleep architecture with effect sizes comparable to the 5 mg/kg CNO condition.

**Conclusions:** Our results demonstrate that the two most commonly used DREADD actuators, CNO and C21, can modulate sleep of mice not expressing DREADD receptors. Sleep modulation through C21 injections, despite a lack of back-metabolism to clozapine, implies that conversion to clozapine is not the sole mechanism underlying side effects of chemogenetic actuators. Therefore, any chemogenetic experiment should include a DREADD-free control group injected with the same CNO, C21 or newly developed actuator. We further suggest that electrophysiological sleep assessment could serve as a sensitive tool to test the biological inertness of novel chemogenetic actuators.

**Disclosure**: No

### O167/P601 | A 40-μg dose of sublingual dexmedetomidine promotes sleep in men with subclinical insomnia

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The anesthetic dexmedetomidine (DMTN) is an α2 adrenoceptor agonist approved for i.v. use in highly-monitored clinical settings. i.v.-DMTN induced sedation may resemble physiological sleep. Attempts of capsule-based, oral DMTN delivery revealed highly variable pharmacokinetics and required 700 μg DMTN to modify sleep. We developed oro-dispersible tablets (ODT) for sublingual DMTN delivery sparing first-pass metabolism, and investigated the pharmacokinetic/pharmacodynamic profile of low μg DMTN administration. We recruited 17 male volunteers (25.5 ± 3.3 years) with subclinical insomnia (8 < ISI < 14) who completed adaptation and three experimental nights separated by one week. At bedtime (11:00 p.m.), we administered 20 and 40 μg DMTN and placebo in randomized, double-blind fashion. To verify DMTN pharmacokinetics during sleep, we collected 18 blood samples from the antecubital vein, connected via extensions to an adjacent room. We quantified DMTN by LC-MS, performed all-

night sleep recordings in the laboratory with SIENNA Ultimate® amplifiers, and examined cardiovascular functions (Schellong test), subjective state and vigilance upon scheduled awakening (7:00 a.m.). Sleep variables were blindly scored (AASM) and analyzed with mixed-model ANOVAs and two-tailed, paired *t*-tests adjusted for multiple comparisons. Maximal DMTN levels of 0.11 ± 0.02 (20 μg) and 0.24 ± 0.06 ng/ml (40 μg) were reached at 1.04 ± 0.39 and 1.48 ± 0.42 h following intake, and half-life times equaled 2.95 ± 0.79 and 3.68 ± 1.90 h, respectively. Total sleep time, sleep efficiency, and all-night durations of N2/N3 sleep did not differ among conditions. Compared to placebo, 40-μg DMTN shortened sleep latency (32.4 ± 4.4 vs. 21.3 ± 3.8 min; $p < 0.05$) and decreased N1 sleep (8.1 ± 1.1 vs. 6.3 ± 0.8 %; $p < 0.005$), and delayed (139.5 ± 20.0 vs. 242.0 ± 19.9 min; $p < 0.0002$) and reduced the occurrence of REM sleep (17.2 ± 1.9 vs. 12.8 ± 1.6 %; $p < 0.00004$). The 20-μg DMTN also reduced REM sleep compared to placebo (14.8 ± 1.2 %; $p < 0.008$). Post-awakening vital signs, subjective state and cognitive performance were not affected. Our innovative ODT formulation demonstrated rapid delivery, precise systemic availability, and highly reliable dose-proportional DMTN concentrations during sleep. Sublingual delivery of DMTN thus provides a powerful tool to study adrenergic mechanisms of sleep-wake regulation, and may be developed to a potent and safe novel approach to treat distinct sleep disorders.

**Disclosure**: No

## O234/P602 | Evaluation of the efficacy of the hypocretin/Orexin receptor agonists TAK-925 and ARN-776 in narcoleptic*orexin/tTa;Tet-O/DTA*mice

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The sleep disorder Narcolepsy, a hypocretin deficiency disorder thought to be due to degeneration of hypothalamic hypocretin/orexin neurons, is currently treated symptomatically. We evaluated the efficacy of two small molecule hypocretin/orexin receptor-2 (HCRTR2) agonists in narcoleptic male *orexin/tTA; Tet-O/DTA*mice.

**Methods:** Male DTA mice ($N = 7$) were 11 ± 1 weeks (23 ± 2 g) at the time of surgery. EEG, EMG, subcutaneous temperature ($T_{sc}$) and activity were recorded by telemetry. TAK-925 (1–10 mg/kg, s.c.) and ARN-776 (1–10 mg/kg, i.p.) were injected 15 min before dark onset in a repeated measures design. Recordings for the first 6-h of the dark period were scored for sleep/wake and cataplexy.

**Results:** Both TAK-925 and ARN-776 caused dose-related delays in the onset of NREM sleep ($F_{(7,\ 42)} = 18.67$, $p = 4.86 \times 10^{-11}$) and REM sleep ($F_{(7,\ 42)} = 6.32$, $p = 4.29 \times 10^{-5}$). Two-way ANOVA indicated significant treatment × time effects on the amounts of Wake ($F_{(35,\ 210)} = 2.79$, $p = 3.17 \times 10^{-6}$), NREM ($F_{(35,\ 210)} = 2.11$, $p = 6.68 \times 10^{-4}$) and REM sleep ($F_{(35,\ 210)} = 2.53$, $p = 2.54 \times 10^{-5}$). At all doses tested, TAK-925 and ARN-776 caused continuous wakefulness and eliminated sleep for the first h. All doses of TAK-925 and all but the lowest dose of ARN-776 eliminated cataplexy during the first h after treatment; the anti-cataplectic effect of TAK-925 persisted into the 2nd h for the highest dose. TAK-925 and ARN-776 also reduced the cumulative amount of cataplexy during the 6-h post-dosing period ($F_{(7,\ 42)} = 3.27$, $p = 0.007$). The acute increase in wakefulness produced by both HCRTR2 agonists was characterized by increased spectral power in the high gamma EEG band during Wake across the 6-h recording ($F_{(7,\ 42)} = 4.91$, $p = 4.09 \times 10^{-4}$). Although neither compound provoked a NREM sleep rebound, both compounds affected NREM EEG during the 2nd h post-dosing. TAK-925 and ARN-776 also increased gross motor activity, running wheel activity and $T_{sc}$, suggesting that the wake-promoting and sleep-suppressing activities of these compounds could be a consequence of hyperactivity.

**Conclusions:** Despite increased activity, the profound wake-promoting and anti-cataplectic activities of TAK-925 and ARN-776 are encouraging for the development of HcrtR2 agonists.

Research supported by NIH R21 NS106882 and R01 NS098813 to T.S.K.

**Disclosure**: No

## O236/P603 | Expression of Hypocretinergic/Orexinergic receptors in hypothalamus and pontine REM sleep-related areas. Plasticity in a pharmacological model with narcolepsy-like features in rats

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**Objectives/Introduction:** The hypothalamic hypocretinergic/orexinergic (Hcrt/Ox) system is involved in many physiological processes including sleep-wake cycle, and its malfunction is involved in narcolepsy. It acts through two G-protein-coupled receptors -Hcrt/OxR1 and Hcrt/OxR2- widely distributed throughout the central nervous system. In the present study we have used suvorexant, a dual Hcrt/Ox receptor antagonist, to block Hcrt/Ox transmission in rats. We have explored Hcrt/OxR1 and Hcrt/OxR2 expression within the hypothalamus, and the dorsal and ventral areas of the oral pontine tegmentum (DOPT and VOPT respectively), known to be involved in REM sleep mechanisms.

**Methods:** In two groups of 8 rats daily i.p. injections of 30 mg/Kg of suvorexant or vehicle (DMSO) were done in the dark period for 7 days. After treatments, Hcrt/OxR1 and Hcrt/OxR2 levels were analyzed by western blotting (Hcrt/OxR1-antibody: ab68718; Hcrt/OxR2-antibody: ab183072) within the hypothalamus, DOPT and VOPT. *T*-tests were used for statistical comparisons.

**Results:** Western blots for Hcrt/OxR2 showed two different -but very close- bands in hypothalamus and VOPT, while only the upper one was observed in DOPT. In the hypothalamus, suvorexant induced a significant overexpression for Hcrt/OxR1 ($t = 2.607$, $p < 0.025$), but not for Hcrt/OxR2 (upper band: $t = 0.576$, $p \leq 0.375$; lower band: $t = 1.537$, $p \leq 0.1$). Regarding the oral pons, under control conditions the levels of the Hcrt/OxR1 were significantly higher in the VOPT than in the DOPT ($t = 3.78$, $p = 0.007$). On the contrary, the levels of the Hcrt/OxR2 upper band were significantly higher in DOPT than in VOPT ($t = 2.383$, $p = 0.0487$). After suvorexant, Hcrt/OxR1 showed a significant overexpression in the VOPT ($t = 2.088$, $p \leq 0.05$), remaining unchanged in the DOPT ($t = 0.401$, $p \leq 0.375$). On the other hand, no significant differences were observed for either of the Hcrt/OxR2 bands in the VOPT between the control and the experimental groups (upper band: $t = 1.259$, $p \leq 0.375$; lower band: $t = 0.182$, $p > 0.4$), while Hcrt/OxR2 in the DOPT showed a significant overexpression after suvorexant ($t = 2.995$, $p \leq 0.005$).

**Conclusions:** The two previously described isoforms of the Hcrt/OxR2 in the mouse may be also present in the rat. Both Hcrt/Ox receptors seem to be involved in narcolepsy pathophysiology, Hcrt/OxR1 mainly at the level of hypothalamus and VOPT, and Hcrt/OxR2 at the DOPT.

**Disclosure**: No

## 2: CELL AND MOLECULAR BIOLOGY AND GENETICS

### O095/P305 | The knockout of glycogen synthase kinase-3 beta in neurons of the mouse cerebral cortex affects electrocorticographic activity during wakefulness and slow wave sleep

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**Objectives/introduction:** Current models propose that vigilance states are regulated, at least in part, by neuronal plasticity. Glycogen synthase kinase-3 beta (GSK3b) is involved in long-term depression and metaplasticity. Also, GSK3b phosphorylates the Fragile × mental retardation syndrome-related protein 1 (FXR1) that has recently been shown to affect homeostatic plasticity and brain activity in response to sleep loss. This project thus aims at investigating the role of GSK3b in wake/sleep regulation by verifying how its localised knockout (KO) in the cerebral cortex of adult normally-developed mice impacts vigilance states under normal (baseline: BL) and sleep-deprived (SD) conditions.

**Methods:** A neuron-specific KO of *Gsk3b* was achieved in adult male mice via viral delivery of a clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system (dual adeno-associated virus [AAV] system) in the motor and visual cortex. AAV injections and electrode implantation for electrocorticography (ECoG) were done simultaneously 3 weeks prior to ECoG recording, which included 24 h BL, 6 h SD, and 18 h recovery. Analyses include vigilance state duration/distribution and ECoG spectral activity for mice with *Gsk3b* AAV-mediated KO mice ($n = 10$) and control AAV-injected mice ($n = 9$). Validation of GSK3b downregulation included immunohistochemistry and spatial transcriptomics, which was also used to investigate sleep-related molecular pathways in *Gsk3b*-KO cortical regions.

**Results:** *Gsk3b* KO did not affect the time spent in each vigilance states nor the alternation between states (*t* tests, $p > 0.05$). However, *Gsk3b* KO decreased gamma (30–50 Hz) activity during wakefulness and alpha (8–10 Hz) activity during slow wave sleep (SWS) in the motor cortex (*t* tests, $p < 0.05$). Moreover, a SD-induced increase in beta and gamma (20–50 Hz) activity during SWS was found in the visual cortex only under *Gsk3b*KO (*t* tests, $p < 0.05$). Spatial transcriptomic data are currently being analysed.

**Conclusions:** These results support a role for GSK3b in the regulation of ECoG activity under BL conditions and in response to sleep loss, and bring a deeper insight on molecular mechanisms controlling vigilance state quality.

**Disclosure**: No

### O096/P306 | HCRTR2 deficiency does not cause cataplexy in mice

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**Introduction:** Orexin/Hypocretin deficiency causes the neurological disease narcolepsy, with excessive sleepiness, state fragmentation, emergence of rapid-eye-movement sleep (REMS)-related states into wake, and cataplexy. Several mouse models phenocopy narcolepsy remarkably well by inactivation of the *Hypocretin* (*Hcrt)* gene, or ablation of Hypocretin neurons. In dogs, several breeds harboring mutations in hypocretin receptor type-2 (*HcrtR2*) exhibit severe narcolepsy. The role of *HcrtR2* in narcolepsy has been a longstanding conundrum. Whether the canine model represents the human disease has never been clarified, although the central role of hypocretin in narcolepsy is undisputed. Whether *HcrtR2*-deficient mice display cataplexy is of major preclinical importance for the understanding of the disease, but remains unclear.

**Methods:** Here we report generation of mice where *HcrtR1*or*2* is inactivated and replaced by *Gfp* ($HcrtR1^{Gfp}$ and $HcrtR2^{Gfp}$), or are doubly ablated ($HcrtR1^{Gfp/Gfp}$; $HcrtR2^{Gfp/Gfp}$). The mice were recorded with EEG/EMG/video polysomnography for 96 h including 48 h of baseline, 6 h sleep deprivation, 42 h of recovery, followed by a chocolate exposure challenge in dark phase.

**Results:** We found that neither $HcrtR1^{Gfp/Gfp}$ or $HcrtR2^{Gfp/Gfp}$ mice display cataplexy, even after exposure to a powerful non-aversive

excitatory stimulus (chocolate) ($n = 9$*HcrtR1*$^{Gfp/Gfp}$, $n = 11$*HcrtR2*$^{Gfp/Gfp}$). Both lines however display sleep attacks (short episode of delta-dominated sleep without complete loss of muscle tone) during the active phase, with or without chocolate, and appear sleepy, with smaller time awake in dark periods. *HcrtR1*$^{Gfp/Gfp}$deficient mice show moreover a pronounced increase in NREM sleep slow-delta activity in light phase, and NREM sleep fragmentation. Cataplexy (sudden loss of muscle tone after a prolonged episode of intense purposeful activity) is only observed in doubly ablated mice ($n = 9$, $n = 5 \pm 2$ cataplexies per 12 h dark phase), a similar incidence as Ox-Ataxin-3 Tg but slightly inferior to the number observed in *Hcrt*-KO mice. Cataplexy in these mice displays the delta-theta EEG signature we priorly described in cataplexy and REMS of *Hcrt*-KO mice.

**Conclusions:** Our findings suggest that cataplexy protection is mediated by an interplay of Hypocretin Receptor 1 and 2 signaling. The data have preclinical relevance for the treatment of narcolepsy and other hypersomnias, and the use of the newly developed selective HCRTR1 and HCRTR2 agonists in these patients.

**Disclosure**: No

## O210/P607 | Obstructive sleep apnea clock (Dys)regulation: Potential applications in OSA diagnosis and treatment?

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**Introduction:** Obstructive Sleep Apnea (OSA) has been recognized as a major health concern worldwide, given its increasing prevalence, difficulties in diagnosis and treatment, and impact on society. Untreated, OSA has been associated with a host of comorbidities, including cardiopulmonary and metabolic disorders. Recent studies suggest that OSA dysregulates the biological clock, which might contribute to the large spectrum of OSA comorbidities. Yet, the interplay between OSA, the clock, and OSA treatment is not fully understood. We proposed to evaluate the impact of OSA and OSA treatment on clock (dys)regulation, and its potential applications in OSA diagnosis and treatment.

**Methods:** We conducted a case-control study involving 34 patients with OSA (age: 55 ± 2), before and after treatment with Continuous Positive Airway Pressure (CPAP), and 7 controls of the same sex and age group (age: 50 ± 3). The levels and temporal profile of clock physiological markers (plasma melatonin and cortisol; body temperature), and the expression of core-clock genes in peripheral blood mononuclear cells, were monitored at four time points along 24 h. Machine-learning methods were applied for data analysis.

**Results:** Patients with OSA showed alterations in the levels and circadian profiles of melatonin and in the expression of several clock genes (e.g., melatonin levels at 8 h: 134 ± 12 pg/ml; *PER1* expression at 22 h30: 0.3 ± 0.2), relative to control subjects (melatonin levels at 8 h: 76 ± 15 pg/ml, $p < 0.01$; *PER1* expression at 22 h30: 1.0 ± 0.2, $p < 0.05$). Two years of CPAP treatment re-established the levels and profiles of melatonin and the expression of some of the evaluated clock genes (melatonin levels at 8 h: 80 ± 17 pg/mL; *PER1* expression at 22 h30: 1.1 ± 0.5). Machine-learning clustering approaches, based on clock-associated markers, distinguished controls from untreated patients (F1 score = 0.95) and showed that long-term CPAP-treated patients better resemble controls than untreated/short-term treated (4 months) patients.

**Conclusions:** OSA disturbs the biological clock. Long-term CPAP has a positive effect, yet it does not fully re-establish the clock. Our results reinforce the need of new/complementary strategies for OSA treatment. Machine-learning approaches, based on clock-associated markers, show potential applications in OSA diagnosis, patient stratification and treatment response monitoring.

**Disclosure**: No

## O230/P608 | Systems biology of mammalian sleep/wake cycles: phosphorylation hypothesis of sleep

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The detailed molecular and cellular mechanisms underlying NREM sleep (slow-wave sleep) and REM sleep (paradoxical sleep) in mammals are still elusive. To address these challenges, we first constructed a mathematical model, Averaged Neuron Model (AN Model), which recapitulates the electrophysiological characteristics of the slow-wave sleep. Comprehensive bifurcation analysis predicted that a Ca2+-dependent hyperpolarization pathway may play a role in slow-wave sleep. To experimentally validate this prediction, we generate and analyze 26 KO mice, and found that impaired Ca2+-dependent K+ channels (Kcnn2 and Kcnn3), voltage-gated Ca2+ channels (Cacna1g and Cacna1h), or Ca2+/calmodulin-dependent kinases (Camk2a and Camk2b) decrease sleep duration, while impaired plasma membrane Ca2+ ATPase (Atp2b3) increases sleep duration. Genetical (Nr3a) and pharmacological intervention (PCP, MK-801 for Nr1/Nr2b) and whole-brain imaging validated that impaired NMDA receptors reduce sleep duration and directly increase the excitability of cells. Based on these results, we propose phoshporylation hypothesis of sleep that

phosphorylation-dependent regulation of Ca2+-dependent hyperpolarization pathway underlies the regulation of sleep duration in mammals. We also recently developed a simplified mathematical model, Simplified Averaged Neuron Model (SAN Model), which uncover the important role of K+ leak channels in NREM sleep. In this talk, I will also describe how we identify essential genes (Chrm1 and Chrm3) in REM sleep regulation, and propose a plausible molecular definition of a paradoxical state of REM sleep.

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**Disclosure**: No

## O231/P609 | Analyses in diversity outbred mice identify new genetic loci associated with sleep phenotypes

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**Objectives/introduction:** Diversity Outbred (DO) mice are a cutting-edge animal model for identifying genetic associations with complex traits. Here, we combine sleep and circadian traits derived from a validated high-throughput phenotyping strategy with genome-wide genotype data in a large number of DO mice to identify new genetic loci associated with sleep phenotypes.

**Methods:** An activity-based phenotyping paradigm was utilized to generate sleep and circadian traits in 535 DO mice. Sleep/wake duration, the number of sleep/wake bouts, and average sleep/wake bout duration were quantified over 5 consecutive days, with sleep defined using a validated criterion of ≥40 s of inactivity. Afterwards, latency to sleep in a new environment (vigilance) and sleep drive on a modified Murine Multiple Sleep Latency Test (m-MMSLT) were derived using validated definitions. Finally, circadian period was quantified based on voluntary wheel-running for 10 days in light/dark followed by 18–20 days in constant darkness. Phenotypes were combined with genome-wide genotype probabilities to perform linkage scans for associated genetic loci.

**Results:** Several new linkage regions (QTLs) for sleep traits were identified. One (chr13:17.53–20.12 Mb) associated with sleep fragmentation; mice with the 129S1/SvlmJ founder allele had more and shorter sleep bouts, whereas mice with the CAST/EiJ or WSB/EiJ founder alleles had longer and fewer sleep bouts. A second (chr3:61.61–67.65 Mb) was associated with sleep drive. Mice carrying the 129S1/SvlmJ allele had faster latency to sleep across m-MMSLT trials, while the CAST/EiJ allele was associated with more resilience to sleep deprivation. A third (chr13:33.48–38.98 Mb) associated with vigilance, with faster latency to sleep in a new environment associated with the A/J haplotype. Supporting more complex genetic effects, no loci were strongly associated with circadian period despite this being one of the most heritable traits in prior analyses in these DO mice.

**Conclusions:** Analyses using DO mice identified novel loci for sleep fragmentation, sleep drive, and vigilance. Downstream studies of gene expression and knock-out mice are required to identify and validate causal genes, in anticipation of translation to disordered sleep in humans. Machine learning approaches targeting epistasis may be required to uncover additional genes explaining heritability of these traits, particularly for circadian period.

**Disclosure**: Yes

**Conflict of Interest statement:** Dr. Churchill and Dr. Svenson disclose that The Jackson Laboratory produces and sells a wide variety of mice for research, including Diversity Outbred mice. All other authors report no financial or nonfinancial conflicts of interest related to the present manuscript. This work was supported by the National Institutes of Health (NIH) grants R01 HL111725, R01 GM070683 and P01 HL094307.

## O232/P610 | Genetic regulation of chromatin accessibility regulation during sleep deprivation

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**Introduction:** Sleep is driven by the interplay of a circadian rhythm and a homeostatic pressure. Though the molecular foundations of circadian rhythm are well understood, understanding of sleep homeostasis is still lacking. We recently published a time course analysis comparing baseline, sleep deprived and recovering mice, highlighting the association between the transcription and chromatin accessibility dynamics. In this study, we identify regulatory regions of the genome associated with response to sleep deprivation (SD) using the BXD genetic reference population of mice.

**Methods:** Chromatin accessibility changes were estimated from cortical ATAC-seq data for 6h sleep deprived (SD) and control animals. 34 BXD/RwwJ recombinant inbred lines, including C57BL/6J (B6) and DBA/2J (D2) parent strains, were used ($n$ ≥ 3/line/condition). Sequencing reads were aligned to the mm10 reference and relevant genomic locations identified based on read count. Genetic effects were estimated by quantitative trait locus (QTL) analysis and SD

effects by generalized linear models corrected for mouse line. Correlations with gene expression were restricted to single topological domains (TD).

**Results:** Widespread changes in chromatin accessibility were found with 36'447 genome regions affected by SD (3.5% of the regulatory genome), 73.5% of which showing increased accessibility. The majority of these regions are correlated with the expression of at least one gene sharing the same TD, with 21% being located 5 Kb of a transcription starting site. Given that different BXD lines respond differently to SD both behaviorally and molecularly, we analyzed the genetic influence on chromatin accessibility, estimating that genetic background (B6 vs. D2 genotype) strongly affected accessibility of 10'308 regions (1.3% of the regulatory genome). Furthermore, 88% of these regions showed significant correlations with expression of genes within the same TD, with 10% being located within 5 Kb of a transcription starting site. Of interest, 25% of the regions showing allelic-specific accessibility overlap with those with changes induced by SD.

**Conclusion:** Our results point to a pervasive and complex interplay between epigenetic and transcriptional factors during SD. We additionally show that genetic background has widespread effects on the epigenetic landscape and transcriptional state, which is fundamental to understand differences in sleep behavior across individuals.

**Disclosure**: No

## 3: ONTOGENY/AGING

### O001/P007 | Wake fragmentation and in vivo posterior hypothalamic integrity in older adults

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**Introduction:** Human aging is accompanied by difficulty to sustain wake states over extended periods of time. Interestingly, wake-promoting neurons of the ascending arousal system appear to be highly vulnerable to age-related neurodegeneration, especially within the posterior hypothalamus. Here, we sought to determine whether wake fragmentation during the day is related to microstructural integrity of the hypothalamus assessed in vivo in a group of healthy, cognitively unimpaired older individuals.

**Methods:** Seventy-eight retired older adults (mean age ± SD = 68.8 ± 5.4 years, 40% female) were included in the analysis. Daytime rest was estimated using actigraphy and calculated as the ratio between the number of epochs classified as rest and the total number of epochs comprised between the mean activity onset time and the mean activity offset time. Concomitantly, the macromolecular content of hypothalamic grey matter tissue was assessed through the combined use of magnetic resonance imaging-derived Magnetization Transfer saturation (MTsat) maps and a recently developed parcellation algorithm of hypothalamic subunits. Generalized linear mixed models were used to test whether daytime rest (outcome) was related to MTsat values within each hypothalamic sub region (predictor).

**Results:** Older age was associated with decreased MTsat values within the hypothalamus ($r = -0.3$, $p = 0.006$). Crucially, after controlling for age, sex, body mass index, and posterior hypothalamic volume, we observed that higher daytime rest is related to lower MTsat values within the posterior hypothalamic region ($F_{1,72} = 5.50$, $p = 0.021$, $R^2_{\beta^*} = 0.07$). This association remained significant after removing the contribution of adjacent mammillary bodies to the posterior hypothalamic MTsat values ($F_{1,72} = 5.26$, $p = 0.024$, $R^2_{\beta^*} = 0.07$), but also when excluding potential confounding effects of transition periods during early morning and late evening hours ($F_{1,72} = 5.20$, $p = 0.025$, $R^2_{\beta^*} = 0.07$).

**Conclusions:** Our results show that the loss of posterior hypothalamic integrity, mainly encompassing wake-active orexinergic and histaminergic neurons, is related to an impaired 24-h rest-activity distribution, and more particularly to an inability to maintain a consolidated period of activity over the classical waking day. This study thereby supports the assumption of a hypothalamic involvement in the stability of sustained activity during wakefulness in humans, as well as the relevance of investigating the sleep-wake cycle as an early lifestyle factor for age-related neurodegeneration.

**Disclosure**: Yes

**Conflict of Interest statement: Disclosure of potential conflict of interest.** The authors have no conflict of interest to disclose.

**Sources of funding:** Belgian Fund for Scientific Research (FNRS/BIG-SLEEP-T022020F), European Research Council (ERC-Starting Grant/COGNAP-GA 757763).

## 4: NEUROBIOLOGY

### O094/P314 | Generating sleep oscillations using primary and hipsc-derived thalamo-cortical cultures

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**Objectives/introduction:** Slow oscillations, delta waves, and spindles are the major brain oscillations during non-rapid eye movement (NREM) sleep, arising from the thalamo-cortical circuitries. Whether the generation of these oscillatory patterns requires subcortical neuromodulatory inputs remain unknown.

**Methods:** Using a high-density microelectrode array with 26,400 electrodes, we recorded both single-unit activity and local field potential (LFP) of primary and hiPSC-derived cortical, thalamic, and thalamo-cortical co-cultures, and assessed their sleep oscillatory patterns.

**Results:** We found that cell assemblies of thalamic ($n = 9$), cortical ($n = 12$), and thalamo-cortical co-cultures ($n = 12$) mimic oscillatory patterns of slow oscillations (<1 Hz), delta waves (2–4 Hz), and spindles (9–16 Hz), respectively, similar to NREM sleep. Interestingly, spindles of thalamo-cortical co-cultures show strong coupling to the slow waves as *in vivo*, and slow waves travel across the cortical culture and are accompanied with fast gamma oscillations, as in the intact brain. Addition to cortical cultures of an antagonist of calcium-activated potassium channels suppressed the slow oscillation, suggesting a subcellular pathway for travelling of these oscillations ($n = 4$). Furthermore, stimulation of these networks using wake-promoting neuromodulators induced desynchronized wake-like states in cultures ($n = 7$).

**Conclusions:** Our results demonstrate that NREM sleep with its oscillatory characteristics is the default state of the cortical and thalamo-cortical networks and highlight the potential applications of developing *in vitro* sleep models to answer basic questions in the field of sleep research.

**Disclosure**: No

## O166/P617 | Reduced numbers of corticotropin-releasing hormone neurons in narcolepsy type 1

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**Objective:** Narcolepsy type 1 (with cataplexy) is a rare invalidating chronic sleep disorder caused by a loss of hypocretin neuropeptides, presumed to be due to an auto-immune process. A systematic search for possible involvement of other hypothalamic neurons implicated in sleep-wake regulation has never been performed.

**Methods:** We systematically quantified immunohistochemically stained sleep-wake-related neuronal populations and the presence of microglia in the hypothalamus of narcolepsy type 1 ($n = 5$) and matched controls.

**Results:** Biological clock: there was no difference in the numbers of vasopressin-expressing neurons in the suprachiasmatic nucleus. Sleep promoting neurons: the density of galanin positive neurons in the ventrolateral preoptic nucleus was stable. Arousal related neurons: we confirmed the hallmark loss of hypocretin-1 expressing neurons and the increased numbers of histaminergic neurons. The density of choline acetyltransferase-expressing neurons in the nucleus basalis of Meynert was unchanged. We found a selective and strong reduction in the number of corticotropin-releasing hormone (CRH)-positive neurons in the paraventricular nucleus (PVN) of narcolepsy type 1 and significantly fewer CRH-positive fibers in the median eminence (Wilcoxon-Mann-Whitney U test (P) $p = 0.016^*$, Benjamini-Hochberg corrections (q) $q = 0.021^*$). While, no alteration was observed in other PVN neurons, that is, vasopressin, oxytocin, or tyrosine hydroxylase--expressing neurons. Microglial reactions: The presence of ionized calcium-binding adaptor molecule 1 tended to be increased in the hypocretin area, but not in any other adjacent area. The human leukocyte antigen-staining was similar in all these areas.

**Interpretation:** This surprising decrease in CRH neurons may contribute to sleep-wake symptoms and may provide novel targets for diagnostics and interventions.

**Disclosure**: No

## O168/P618 | Locus coeruleus reactivity during wakefulness is associated with REM sleep intensity

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**Introduction** The locus coeruleus (LC) is the main source of norepinephrine (NE) in the brain and sends widespread projections over almost the entire brain. The LC-NE system is involved in regulating a broad range of brain functions and processes, including arousal and sleep regulation. It plays key roles in the generation and regulation of REM sleep. Whether the LC underlies part of the inter-individual variability in human sleep is not established, however. Here, we tested whether the reactivity of the LC during wakefulness, as well as some of its structural characteristics were associated with the sleep quality of healthy younger and older individuals.

**Methods** We conducted high resolution 7 Tesla functional Magnetic Resonance Imaging (7 T fMRI) in healthy younger ($N = 24$; age: 22.1 y ± 2.7) and late middle-aged ($N = 19$; age: 61.4 y ± 5.1) individuals performing an auditory oddball task. Based on a structural acquisition sensitive to the neuromelanin content of the LC, which allowed its precise delineation, we computed LC volume and LC neuromelanin contrast and extracted LC activity associated with the detection of deviant tones during the oddball task, which we took as an index of LC reactivity. Nighttime habitual sleep was recorded in-lab under electroencephalography (EEG). Following automatic sleep scoring, we extracted several sleep features including cumulated theta (4–8 Hz) power during REM sleep and sleep onset latency (SOL). Generalized additive models (GAM), controlling for sex, age and BMI, sought linear and non-linear associations between sleep features and LC characteristics.

**Results** Statistical analyses ($N = 43$) first revealed a significant linear association linking higher reactivity of the LC during wakefulness to lower theta power during REM sleep ($p = 0.03$). Analyses also yielded a significant non-linear association between larger LC volume and reduced REM theta power ($p = 0.017$). We further found that shorter SOL was linearly associated with reduced LC reactivity and volume ($p = 0.03$; $p < 0.0001$).

**Conclusions** These findings provide unique *in vivo* insight on the mechanisms regulating sleep in humans. They may bring important implications for insomnia patients, which are hypothesized to present abnormal LC activity during sleep. We expect that ongoing data collection will confirm these preliminary results.

**Disclosure**: No

## O188/P619 | The effect of nocturnal neural and endocrine activity on amyloid-beta fluctuations

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**Introduction:** Recent evidence points towards a metabolic function of slow-wave sleep (SWS), suggesting that during this stage, the brain is cleared from potentially toxic metabolites, such as amyloid-beta. Poor sleep or elevated cortisol levels can adversely affect amyloid-beta clearance, potentially leading to the formation of amyloid plaques, a neuropathological hallmark of Alzheimer's disease. Here, we explore how nocturnal neural and endocrine activity affects amyloid-beta fluctuations in the peripheral blood as a reflection of cerebral clearance.

**Methods:** Simultaneous polysomnography and all-night blood sampling were acquired in 60 healthy volunteers aged 20–68 years old. Plasma concentrations of two amyloid-beta species (amyloid-beta-40 and amyloid-beta-42), cortisol and growth hormone were assessed for every 20 min of sleep. Amyloid-beta fluctuations were modeled using linear and generalized additive mixed-effects models with sleep stages, oscillatory and non-oscillatory power, and hormones as predictors while controlling for age and multiple comparisons. Time-lags between the predictors and amyloid-beta ranged from 20 to 120 min.

**Results:** The amyloid-beta-40 and amyloid-beta-42 levels correlated positively with growth hormone concentrations, SWS proportion, slow-wave (0.3–4 Hz) oscillatory and high-band (30–48 Hz) non-oscillatory power, but negatively with cortisol concentrations and REM sleep proportion. The significant results were obtained only for the models using the 40–100 min lags (all $t$-values > |3|, $p$-values < 0.003). Amyloid-beta-40, but not amyloid-beta-42 levels positively correlated with the participants' age.

**Conclusions:** Slow-wave oscillations are associated with higher plasma amyloid-beta levels, reflecting their contribution to the cerebral amyloid-beta clearance, possibly via the coupling with blood and cerebrospinal fluid flow. REM sleep is related to decreased amyloid-beta plasma levels; however, this link may reflect passive aftereffects of SWS and not REM's effects per se. Strong associations between cortisol, growth hormone and amyloid-beta presumably reflect the sleep-regulating role of the corresponding releasing hormones and may serve as a new marker of clearance efficiency. A positive association between age and amyloid-beta-40 may indicate that peripheral clearance becomes less efficient with age. Our study provides important insights on the specificity of different sleep features' effects on brain clearance and establishes concurrent polysomnography and all-night blood sampling as a promising tool for investigating the significance of metabolites' clearance in health and neurodegeneration.

**Disclosure**: No

## O233/P620 | Glutamate neurons in the sublaterodorsal tegmental nucleus regulate REM sleep homeostasis

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**Introduction:** We have previously shown that glutamate sublaterodorsal-tegmentum (SLDGLUT) neurons control multiple aspects of REM sleep; however, it remains unknown whether they also play a role in REM sleep homeostasis. REM sleep homeostasis is defined by the fact that REM sleep pressure builds-up during inter-REM interval and is dissipated during REM sleep. Hence, it requires a longer time following a long REM sleep period to accumulate enough pressure to trigger the next REM sleep episode. Here, we aimed to determine whether the activity of SLDGLUT cells reflects REM sleep homeostasis, and how optogenetic manipulation of these cells influences the duration of inter-REM intervals.

**Methods:** We injected an AAV containing the calcium indicator GCaMP7f in the SLD of 7 vGLUT2-Cre mice to monitor the activity of SLDGLUT cells. Then, to manipulate SLDGLUT neurons activity, we bilaterally infused an AAV containing either a light-sensitive inhibitory opsin (AAV-EF1α-DIO-ARCH-eYFP) or a light-sensitive excitatory opsin (AAV- EF1α-DIO-ChETA-eYFP) or an inert control protein into the SLD of 15 vGLUT2-Cre mice.

**Results:** To determine whether the activity of SLDGLUT neurons reflects REM sleep homeostasis, we monitored the fluorescent changes (ΔF/F) indicative of Ca2+ transients of SLDGLUT cells. We found that Ca2+ transients in GCaMP7f-expressing SLD neurons was maximal during REM sleep ($n = 7$, $p < 0.001$) and correlated with the duration of REM sleep ($n = 121$, $r = 0.95$, $p < 0.001$). Importantly, we found that the activity of SLDGLUT neurons during the inter-REM interval following long REM sleep episode (>40 s) was lower compared to the activity following shorter ones (≤40 s), suggesting a stronger dissipation of REM sleep pressure following long REM sleep episode ($n = 7$, $p < 0.001$). Finally, we found that light-activation of

SLDGLUT cells did not increase inter-REM intervals ($n = 5$, 50 REM episodes, $p = 0.9995$) despite increasing the duration of the preceding REM sleep ($p < 0.01$), while light-silencing increased inter-REM intervals ($n = 5$, 23 REM episodes, $p < 0.01$) without changing the duration of the preceding REM sleep ($p = 0.9973$).

**Conclusion:** Our data demonstrate that the activity of SLDGLUT cells reflects REM sleep homeostasis, and manipulation of their activity directly affects REM sleep timing despite changes in REM sleep pressure. Hence, we conclude that SLDGLU cells regulate REM sleep homeostasis.

**Disclosure**: No

## O235/P621 | Perception of safety-danger across sleep-wake state

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Sleep is associated with a sensory disconnection from the environment, thought to be mediated by a thalamic gating of sensory-motor processing. However, recent studies suggested that the gate is located downstream of thalamic relays, yet the underlying mechanisms remain unclear. Here, we investigated 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 from chronically implanted electrodes in primary auditory cortex (Au1), central medial thalamus (CMT), dorsal medial geniculate (dMG), and hippocampus (HP) in freely-moving wild-type mice ($n = 5$). We found similar auditory stimuli-evoked LFP responses during wakefulness and REM sleep whereas their amplitude was higher during NREM sleep. Furthermore, we showed that animals 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, confirmed by optogenetic silencing ($n = 10$, unpaired $t$-test $p < 0.05$) and a computational approach. Finally, to test whether the information associated with auditory cues–that is, 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 (WT group: no-opto $n = 5$; NREMs-specific group: $n = 6$ ArchT and $n = 5$ YFPs; REMs-specific group: $n = 5$ ArchT and $n = 5$ YFPs). Our results showed a significant increase in the percentage of awakening from the CS+ after the conditioning (paired $t$-test $p < 0.05$), suggesting that the discriminative ability persisted during NREM, but not, REM sleep. Interestingly, the CMT opto-silencing compromises this stimuli discrimination, decreasing significantly (paired $t$-test $p < 0.05$) the percentage of awakening specifically for the cued-stimuli (CS+). Taken together, our results showed that CMT neurons are central to the processing of environmental auditory cues associated with danger.

**Disclosure**: No

# 5: PHYSIOLOGY

## O098/P321 | Orexin mediates neuromodulation during sleep

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**Objectives:** Orexin (hypocretin) neurons are important for sustaining long periods of wakefulness and their activity is linked to a variety of behaviors including feeding, motivation and reward processing. However, the role of orexin in the regulation of sleep and its components remains elusive as it was hypothesized that orexin neurons are silent during sleep.

**Methods:** We investigated orexin neurons of the lateral hypothalamus using "*in vivo*" fiber photometry imaging in Hcrt-IRES-Cre mice ($n = 6$), noradrenergic activity of locus coeruleus (LC) in Dbh-IRES-Cre mice ($n = 6$), and LC noradrenergic activity in orexin-knockout/Dbh-Cre mice ($n = 3$), combined with EEG/EMG recordings, during baseline and after sleep deprivation.

**Results:** We found that the activity of orexin neurons correlates with the phasic components of REM sleep, in particular at enhanced power and faster frequency of theta rhythm, and reaches its highest levels prior to the termination of REM sleep episodes. Furthermore, we found that LC noradrenergic system is periodically reactivated during NREM sleep, as reported recently by other groups, but LC reactivations during NREM sleep are more frequent in orexin-knockout mice compared to controls. Additionally, the duration of each NREM LC reactivation after sleep deprivation is several-folds longer than during baseline NREM sleep.

**Conclusions:** Our results suggest a strong role for the orexin system in the regulation of REM sleep theta oscillations and the termination of REM episodes, as well as mediating neuromodulatory effects during NREM sleep.

**Disclosure**: No

## O163/P628 | Pulse-modulated 5 g radio-frequency electromagnetic fields affect the non-rapid-eye-movement sleep electroencephalogram in a ***CACNA1C*** genotype-dependent manner

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**Objectives/Introduction:** The effects of latest standard (5G) pulse-modulated, radio frequency electromagnetic fields (RF-EMF) on the sleep electroencephalogram (EEG) are unknown. Signals of older RF-EMF standards typically enhanced alpha/sigma activity in NREM sleep

with high individual variability. Hypothesized molecular mechanisms underlying the impact of RF-EMF exposure on brain functions include voltage-gated calcium channels (VGCC). We investigated whether 5G RF-EMF signals affect the sleep EEG, and whether a genetic variant of *CACNA1C*, encoding a L-type calcium channel underpinning ~9–15 Hz EEG oscillations *in vitro* and *in vivo*, modulates these effects.

**Methods:** Based on polymorphism rs7304986 of *CACNA1C*, we prospectively selected two groups of healthy young volunteers, individually matched for sex and age (15 T/C genotypes; 19 T/T genotypes). In randomized, double-blind fashion, we applied three standardized, 30-min RF-EMF exposures to the left cerebral hemisphere starting 60 min before bedtime: "E7" = 700 MHz carrier frequency, 20 MHz bandwidth; "E3" = 3.6 GHz carrier frequency, 100 MHz bandwidth; "S0" = sham. Both active fields exhibited 10–14 Hz modulation and peak spatial specific absorption rate of 2 W/kg averaged over 10 g (head tissue). We blindly processed, scored and analyzed the high-density EEG recorded during sleep as previously described. We restricted the current analyses to channels C3-A2/C4-A1 and non-rapid-eye-movement (NREM) sleep, and computed linear mixed models using stepwise regression, followed by student's *t*-tests.

**Results:** The RF-EMF exposure reduced NREM sleep EEG power density bilaterally in most 0.25-Hz bins between 0–25 Hz. Interestingly, the effects on the 14.25–16.0 Hz band revealed an interaction between "exposure" and "genotype". Sigma activity in the first hour of NREM sleep was reduced in both hemispheres and after both exposures in T/T ("E3": $p_{C3} < 0.006$, $p_{C4} < 0.03$; "E7": $p_{C3} = 0.06$, $p_{C4} < 0.05$), but not T/C genotype participants. We observed similar effects of exposure and genotype when all-night spectra were analyzed.

**Conclusions:** Our first exploratory analyses of central leads indicate that in contrast to older RF-EMF standards, two realistic 5G RF-EMF signals reduced rather than increased EEG sigma activity in NREM sleep. The impact of *CACNA1C* genotype on the sleep EEG changes suggests that VGCC could be involved in mediating these effects.

**Disclosure**: No

**Conflict of Interest statement:** The work was supported by the Swiss Federal Office of the Environment and institutional funds.

## O164/P629 | Slow wave energy and sleep onset latency are related by brainstem myelin in healthy young men

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**Objectives/introduction:** The association between sleep variability and regional myelination of subcortical brain structures remains largely unexplored in humans. Here, we examined association of brainstem grey matter myelin with variability in healthy sleep.

**Methods:** In this prospective observational study, in-lab EEG recordings of habitual sleep and quantitative MRI (qMRI) were conducted on 321 young men (18–31 y; 22.1 y ± 2.7). Automatic procedures were used to score sleep stages, detect artefacts and arousals and extract EEG power in NREM delta (.5–4 Hz) and REM theta (4–8 Hz). qMRI data were processed using hMRI toolbox in SPM12 to compute magnetization transfer saturation (MTsat), a parameter directly related to myelin content, over the so-called monoaminergic gray matter compartment (mGM) of brainstem, containing nuclei such as the locus coeruleus and dorsal raphe. Generalized Additive Model for Location, Scale and Shape (GAMLSS) were used for statistical analyses seeking associations between sleep parameters and MTsat, while controlling for age, BMI, sleep duration and intracranial volume.

**Results:** Separate GAMLSS with slow wave energy (SWE, cumulated overnight NREM delta power) or sleep onset latency (SOL) as dependent variable revealed significant main effects of MTsat and interactions between MTsat and age (SWE: main effect MTsat, $\beta$: 43.6, $p = 0.009$; MTsat-by-age interaction: $\beta$:−1.9, $p = 0.01$. SOL: main effect MTsat, $\beta$: −45.6, $p < 0.0001$; MTsat-by-age, $\beta$: 2.0, $p < 0.0001$). The associations remained significant even after adding the significant association we detected between SWE or SOL and medial prefrontal cortex (mPFC) MTsat (SWE: main effect MTsat mPFC: $\beta$: 24.1, $p = 0.005$; SOL: main effect MTsat mPFC: $\beta$: −17.2, $p = 8.07E\text{-}05$), ruling out cortical myelin influence. Age-group analysis showed that the interaction between MTsat and age was mainly driven by individuals aged 24–31 y which showed decrease in SWE and increase in SOL with increased MTsat values. None of the other sleep parameters were significantly associated with MTsat values.

**Conclusions:** Our findings show that higher regional brainstem myelin content is associated with SWE and SOL in an age specific manner in healthy young men. These findings suggest that myelination of brainstem which contain many reticular nuclei essential to sleep-wake regulation, may shape part of individual sleep characteristics.

**Disclosure**: Yes

**Conflict of Interest statement:** Support: FNRS, ULiège, Wallonia-Brussels Federation, EUFEDER program, WELBIO, Clerdent Foundation, Alzheimer Foundation (SAO-FRA), Leon Frédéricq Foundation.

## O165/P630 | Cortico-cortical and thalamo-cortical connectivity during non-REM and REM sleep: Insight from intracranial recordings in human

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**Objectives:** The aim of this study was to study changes of thalamo-cortical and cortico-cortical connectivity during wakefulness, non-Rapid Eye Movement (non-REM) sleep, including N2 and N3 stages,

and REM sleep, using stereo electroencephalography (SEEG) recording in humans.

**Methods:** We studied SEEG recordings of ten patients with drug-resistant focal epilepsy during wakefulness, non-REM sleep and REM sleep, in seven brain regions of interest including the thalamus, temporal regions (mesial and lateral), parietal regions (mesial and lateral), prefrontal cortex and insula. Cortico-cortical and thalamo-cortical connectivity was measured, calculating directed and undirected functional connectivity using a measure of non-linear correlation coefficient $h^2$.

**Results:** The thalamus was more connected to other brain regions during N2 stage and REM sleep than during N3 stage during which cortex was more connected than the thalamus. We found two significant directed links: the first from the prefrontal region to the lateral parietal region in the delta band during N3 sleep and the second from the thalamus to the insula during REM sleep.

**Conclusions:** These results showed that cortico-cortical connectivity is more prominent in N3 stage than in N2 and REM sleep. Therefore, we found a pattern of cortical connectivity during N3 sleep concordant with antero-posterior traveling slow waves already described in the literature. During REM sleep we found significant thalamo-insular connectivity, with a driving role of the thalamus, suggesting that the thalamus is particularly involved as a hub of connectivity during REM sleep.

**Disclosure**: No

### O190/P631 | Association of alzheimer's disease genetic risk and EEG features of the awake brain in healthy young men

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**Objectives/Introduction:** A bidirectional detrimental link emerges in the literature between sleep and Alzheimer's disease (AD) neuropathology. This link is evident in young adults in which the genetic liability for developing AD has been associated with features of sleep electroencephalography (EEG) (Muto et al. 2021 SLEEP). Whether features of the EEG of the awake brain may be related to AD genetic risk is not established. Our goal was to assess whether genome-wide polygenic risk scores (PRS) for AD is associated with EEG recordings acquired during wakefulness in healthy young adults, decades before typical AD symptom onset.

**Methods:** A total of 364 young healthy men (aged 18–31 y) were enrolled in a protocol that included 40 h sleep deprivation carried out under constant routine conditions during which EEG recordings of quiet spontaneous brain activity were completed every 2 h. The signal of Fz channel was used to compute relative power over the typical bands of the EEG in each session. The present analyses only focused on the average relative power of daytime recordings (1-to-9 h after wake-up time). Individual PRS for AD was estimated using the summary statistics of a large AD case-control study. Statistical analyses consisted of generalized additive models (GAM) to test for linear and non-linear associations between EEG power metrics and individuals PRS, including age and BMI as covariates.

**Results:** GAMs yielded significant nonlinear associations between relative power in the theta (4–8 Hz) and in the alpha (8–12 Hz) bands and PRS for AD (theta: $p < 0.0001$; alpha: $p < 0.0001$). Inspection of the non-linear relationship indicated that lowest PRS were associated with lower relative alpha and theta power while highest PRS were associated with higher relative alpha and theta power. In contrast, the broad range of intermediate PRS were not associated with theta or alpha power.

**Conclusions:** These preliminary results highlight that the genetic risk for AD may be associated with features of the EEG of the awake brain related to sleepiness (theta) and cortical excitability (alpha). Future analyses will consider the EEG dynamics over the entire 40 h sleep deprivation protocol.

**Funding:** FNRS, ULiège, EU-FEDER, Alzheimer foundation (SAO-FRA), Wallonia-Brussels federation, Welbio, Baron Clerdent Foundation

**Disclosure**: No

## 6: CHRONOBIOLOGY

### O106/P329 | Exposure to a metameric display backlight affects the incidence of slow eye movements

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**Introduction:** Visual displays emit optical radiation at short wavelengths, close to the peak sensitivity of melanopsin. The strength of non-image forming (NIF) responses to light depend on the "melanopic equivalent daylight illumination - mEDI. Thus, here we investigated effects of spectral changes of a display backlight on the incidence of slow eye movements (SEMs), an objective measure for sleepiness in humans.

**Methods:** Spectrally different white lights that are perceived as the same white tone are called metamers. We developed a metameric display backlight with 5 LED-types (440, 480, 500, 550 and 620 nm). By shifting the peak wavelengths of the primary colors, equal stimulation

of the three cone types but different stimulation of melanopsin (high [HM] and low [LM] [factor "condition"]) was achieved. Seventy-two healthy male participants were examined two times (HM and LM) under controlled laboratory conditions in a randomized within subject design. Participants were divided into 4 luminance groups.

- Group 1: Luminance 27 cd/m$^2$, HM mEDI 15 lx, LM mEDI 4 lx
- Group 2: Luminance 62 cd/m$^2$, HM mEDI 33 lx, LM mEDI 9 lx
- Group 3: Luminance 135 cd/m$^2$, HM mEDI 70 lx, LM mEDI 21 lx
- Group 4: Luminance 284 cd/m$^2$, HM mEDI 146 lx, LM mEDI 48 lx

The incidence of SEMs, derived from the Electrooculography (EOG) were quantified every 30 ss during the 3.5-h of light exposure period and averaged across 30-min bins. We analysed the resulting data using Generalized Linear Mixed Models (PROC GLIMIX) with the factors condition and time.

**Results:** Data of 72 volunteers entered statistical analysis. For all groups the factor "time" was significant ($p < 0.001$). Group 1, 2 and 4 showed significantly more SEMs during LM than HM ($p < 0.001$), ($p = 0.015$) and ($p < 0.001$) respectively, but not group 3.

**Conclusions:** Depending on their mEDI, commonly experienced display luminance's affect objective sleepiness as indexed by the occurrence of SEMs. To decrease alerting effects of light before bedtime without changing the perceived white tone, reducing mEDI of electronic displays at typical luminance's is a successful approach.

**Disclosure**: No

## O107/P330 | Characterisation of pupil responses to alternating light intensities across different cognitive tasks

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Besides vision, light bears many non-image forming (NIF) functions such as the ability to stimulate cognition and alertness, and regulate sleep. Another effect of light NIF is pupil size modulation which offers an easily accessible readout of the physiological impact of light. Here, we aimed at characterising the pupil responses to different melanopic light levels during a fMRI protocol to determine its quality in assessing NIF effects of light on brain functions.

Pupil diameter was continuously recorded in 15 healthy participants (24.7 y ± 2.7; 10 women) via an eye tracker device while they were consecutively administered 3 distincts auditory cognitive tasks (15-, 20- and 25-min long) in a ultra-high-field 7 T MRI scanner. Tasks respectively probed attentional, executive, and emotional processes. Participants were concomitantly exposed to pseudo-randomly alternating 30 s blocks of blue-enriched (4,000K; 3 intensities: 63, 155, 308 melanopic EDI lux) and orange (589 nm; 0.2 melanopic EDI lux) lights separated by 15 s darkness periods. Statistics consisted of generalised linear mixed models that sought to measure the effects of light melanopic level on pupil response, with subjects as random intercept and controlling for age, sex and BMI.

Higher melanopic level exposure was significantly associated with smaller pupil diameter, across all three tasks (main effect of melanopic level: $F > 140$; $p < 0.0001$). The impact of the light melanopic level on pupil size did not significantly change over the three tasks (light melanopic level × task: $F = 0.15$; $p = 0.988$), suggesting that the nature of the task and prior light blocks did not influence pupil constriction. An effect of time was significantly related with a smaller pupil response (main effect of task: $F = 6.6$; $p = 0.002$).

Higher melanopic level light triggers a stronger pupil response while pupil response remains stable across tasks, including alternating short light and darkness exposures. Protocol duration, most likely associated with participant fatigue or boredom, suggests a smaller pupil response in time. These findings support the validity of the protocol to characterise light impact on cognition through 3 auditory tasks using fMRI. We now aim to include more participants to assess the generalisation of the present findings to other age-ranges.

**Funding: ULiège, UMaastricht, LIGHTCAP EU-ETN-MSCA, FNRS, Léon-Frédéricq-Foundation**

**Disclosure**: No

## O108/P331 | Light targeting the melanopic system suppresses melatonin, but does not alter sleepiness, vigilance, sensory processing, or sleep

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**Objectives:** Pre-sleep exposure to especially short-wavelength light (i.e., 460–480 nm) acutely suppresses melatonin, increases vigilance, and decrease sleepiness. Activating effects can also extend to sleep resulting in for instance decreased slow wave activity. The latter effects have mainly been attributed to melanopic effects of light on intrinsically photosensitive retinal ganglion cells (ipRGCs), but definite mechanistic answers are missing. Thus, we here investigated for the

first time whether two metameric light conditions designed to exclusively differ in their melanopic effects (123 vs. 59 lux melanopic EDI) also differentially affect sleep besides neuroendocrine melatonin effects. Beyond this, we also studied whether the light conditions differentially modulate sensory processing during wakefulness and subsequent sleep.

**Methods:** In a preregistered study, twenty-nine healthy participants aged 18–30 years (15 women) were exposed to two metameric light conditions (high- vs. low-melanopic, differing by a factor of 2×, 7-day washout period) for one hour prior to their habitual bed time. Light exposure was followed by an 8-h sleep opportunity with full polysomnography. Objective sleep assessments were complemented by self-reported sleep evaluation after wake-up. Vespertine salivary melatonin levels, subjective sleepiness, and behavioural vigilance were assessed in regular intervals. Sensory processing was evaluated using an oddball paradigm participants completed during the light exposure in the evening and the following sleep period. Specifically, we were interested in neural responses (i.e., event-related potentials [ERPs]) to violations of expectations, that is, the mismatch response. For statistical analyses, we used standard non-parametric analyses except for ERPs, which were evaluated a using cluster-based permutation approach.

**Results:** Despite melatonin suppression by about 14% in the high- compared to the low-melanopic condition, light conditions did not differentially affect sleepiness, behavioural vigilance, objectively assessed sleep, or self-perceived sleep quality. A neural mismatch response was evident during wakefulness and all sleep stages and neither differentially modulated by light.

**Conclusions:** Light targeting the melanopsin system suppresses melatonin, but does not necessarily translate to altered levels of vigilance or sleepiness. Neither does it induce differential changes in sleep (quality), or basic sensory processing. This suggests that an interaction between melanopsin and cone-rod signals might be responsible for such effects to occur.

**Disclosure**: Yes

**Conflict of Interest statement:** CC and MS declare the following interests related to lighting. MS is currently an unpaid member of CIE Technical Committee TC 1-98 ("A Roadmap Toward Basing CIE Colorimetry on Cone Fundamentals"). MS was an unpaid advisor to the Division Reportership DR 6–45 of Division 3 ("Publication and maintenance of the CIE S026 Toolbox") and a member of the CIE Joint Technical Committee 9 on the definition of CIE S 026:2018. Since 2020, MS is an elected member of the Daylight Academy, an unpaid member of the Board of Advisors of the Center for Environmental Therapeutics. MS is named inventor on a patent application entitled on optimising non-linear multi-primary LED system filed by Oxford University Innovation Ltd. (US Patent Application no. 17/428,073, European Patent Application No 20705492.5). CC has had the following commercial interests related to lighting: honoraria, travel, accommodation and/or meals for invited keynote lectures, conference presentations or teaching from Toshiba Materials, Velux, Firalux, Lighting Europe, Electro Suisse, Novartis, Roche, Elite, Servier and WIR Bank. CC is a member of the Daylight Academy.

## O109/P332 | Light-induced chronic phase-shift drives to circadian time-dependent cognitive and emotional alterations

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**Introduction**: Exposure to irregular light cycle, as experienced in shift work, has dramatic influence on cognitive and emotional functions. According to a recent study, memory and mood alterations of mice exposed to T7 ultradian cycle (3.5 h light/3.5 h dark) would result from direct, non-circadian, photic effects, although changes in circadian rhythm activity were observed. Our aim was to determine whether memory and mood alteration observed under ultradian light-dark cycle (T7) is the consequence of the direct effects of light and/or changes in circadian drive.

**Methods**: Sleep of adult male C57BL/6 mice was recorded continuously using electrocorticography and electromyography during two baseline days under T24 cycle (12 h light/12 h dark) and then during 13 days of T7 cycle ($n = 6$). Memory abilities were assessed using spatial novelty preference test (SNPT) in T-maze ($n = 11$–13). The tests were performed twice, at the end of the day under T24 cycle (ZT9) and 13 days later after being exposed to different light schedules (T24 or T7) and performed at different time points (CT21 or CT9). Depression-like behaviour (response to an aversive and inescapable situation) was evaluated using tail suspension test at ZT9 under T24 exposure. Because it is not possible to perform this test twice, this behaviour was evaluated again using the forced swim test (FST), performed after 12 days under T24 or T7 cycle (CT21 or CT9, $n = 10$–12).

**Results**: We first confirmed that T7 cycle induced a chronic phase-shift of both general activity and sleep by (1) lengthening the period and (2) through direct light effects inhibiting activity and promoting sleep. SNPT demonstrated that cognitive deficit appears only at CT21 in mice exposed to T7. In the same condition, mice also showed an alteration of their reaction face to an acute stressor in the FST.

**Conclusion**: Therefore, our data demonstrated that light-induced chronic phase-shift drives to cognitive and emotional alterations that do not depend on direct effects of light, but are observed at specific time of day. These results are of critical importance for both medical and societal applications and will help better understanding cognitive

and mood alterations observed in circadian rhythm sleep-wake disorders.

**Disclosure**: No

## O110/P333 | Characterising transient pupil response to sensory inputs under different light conditions

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**Introduction:** Light has many non-image-forming (NIF) functions including stimulation of cognition and alertness, potentially through an impact on the brainstem locus coeruleus (LC). Transient dilation in pupil size in response to sensory input is considered to be primarily driven by LC phasic activity. Whether this transient pupil dilation is affected by light NIF effects is not established. Before, determining how ambient light affect activity of the LC with fMRI analysis, we aimed at characterising the transient pupil response under different light conditions.

**Methods:** Pupil diameter was recorded continuously in 9 healthy subjects (20–30 y, 7 women) with an eye tracking device while they completed a 15–18 min auditory emotional task during a 7 T fMRI scan. During the task participants listened to emotional and neutral stimuli whilst exposed to pseudo-random alternating 30–40 s blocks of polychromatic, blue-enriched light (63, 155, 308 melanopic EDI lux) and monochromatic orange light (589 nm; 0.2 melanopic EDI lux). The transient pupil response was computed as the change in the pupil size from before and after the stimulus presentation. Statistical analysis consisted of a generalised linear mixed model (GLMM) with transient pupil response as the dependent variable seeking for effects of the light and emotional conditions, with subjects as random intercept and sex and age as covariates.

**Results:** The GLMM revealed a significant effect of the light condition ($F[4,22.9] = 16.7$, $p < 0.0001$) indicating that the transient pupil response was greater under higher levels of blue-enriched light. Despite qualitative differences between the emotional conditions, GLMM did not yield difference between neutral and emotional stimulations ($F[1,22.9] = 0.4$, $p = 0.5$). Furthermore we did not observe a significant interaction between light and emotional conditions ($F[4,22.9] = 1.1$, $p = 0.4$).

**Conclusions:** We report preliminary results demonstrating that despite the sustained pupil constriction induced by prolonged light exposure, transient pupil responses to auditory stimulation (which is presumably driven by LC phasic activity) is increased by light level, and potentially particularly if its blue light content is higher. We aim to add more participants to this analysis and to characterise the LC's activity to light during an fMRI protocol concomitant to pupil measurement.

**Disclosure**: No

## O111/P334 | Sensitivity of the pupillary light reflex to the spectrum of evening light in children and adolescents

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**Objectives/introduction:** The pupillary light reflex (PLR) has been identified as a marker of circadian sensitivity to light. In adults, pupil constriction is significantly greater and more sustained after exposure to blue light compared with red light, and the PLR under blue light is associated with concurrent disruptions to circadian timing. Extending these findings to children and adolescents, we assessed the PLR in response to evening light of different wavelengths as a first step toward identifying differences in circadian sensitivity to blue vs. red light.

**Methods:** Healthy good-sleeping participants aged 8.0–9.9 years ($n = 21$) or 15.0–16.9 years ($n = 11$) maintained a stable sleep schedule for 5 days. On the final day of the protocol, participants remained indoors wearing dark glasses to limit bright light exposure and reduce variability in light history, followed by an in-lab evening PLR assessment. Participants experienced two counterbalanced experimental conditions: a blue (459 nm) and red (627 nm) light exposure in the hour before their scheduled bedtime. After 1 h of a dim-light adaptation (<1 lux), we measured pupil diameter during a 30 s baseline, 10 s light exposure ($3.0 \times 10^{13}$ photons/cm$^2$/s), and 40 s recovery. Following a 7-min dim-light re-adaptation, the procedure was repeated for the other condition. We examined the impact of lighting condition on percent maximum pupil constriction during the light exposure and recovery during the first 10 s after light offset.

**Results:** Within each age group, maximum pupil constriction was significantly larger in response to blue light compared with red light (children: blue = 57.5%, red = 55.8%, $p = 0.004$, $d = 0.70$; adolescents: blue = 55.3%, red = 52.9%, $p = 0.002$, $d = 1.30$). Additionally, in the 10 s after light offset, pupil diameter exhibited a slower return to baseline for blue light in both children ($p = 0.005$, $d = 0.70$) and adolescents ($p = 0.002$, $d = 1.24$). No differences were observed between age groups.

**Conclusions:** In school-aged children and adolescents, exposure to blue light elicited a greater and more sustained pupillary response than red light in the hour before bedtime. This suggests that evening exposure to blue light may be more impactful on the circadian system than red light across development. Future research will examine the

association between the PLR and circadian sensitivity (i.e., melatonin suppression and circadian phase shift) in children.

**Disclosure**: No

## O145/P335 | Evidences of a post-REM sleep refractory period in the ultradian organization of the sleep-wake cycle obtained in two separate rodent lineages

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**Introduction:** The architecture of the sleep-wake cycle of mammals exhibit a specie-specific organization whose atomic building block is the ultradian sleep cycle. The ultradian sleep cycle has been described as a binary structure composed by a REM sleep episode (REMep) and the adjacent interval without REM sleep (INT) that contains variable amounts of wakefulness and NREM sleep. A short-term hourglass mechanism has been proposed to explain the relationship between the duration of the REMep and the duration of the following INT. Park et al. (2020) found evidences in mice for a REM sleep refractory period (RSRP) occurring after consolidated REMep, whose duration is directly proportional to the duration of the REMep that may underlie the short-term hourglass mechanism. By reproducing Park's strategy we explored the existence of a RSRP in the ultradian organization of two rodent species of separate lineages.

**Methods:** Data were obtained in chronically implanted albino rats ($n = 29$, 62 recording days) and degus (*Octodon degus*; $n = 15$, 1560 recording days) maintained under 12:12 LD cycle. Sleep was manually scored and REMep and INT identified.

**Results:** A total of 5298 and 2734 utradian cycles (REMep+INT) was obtained for rats and degus respectively. Statistics were performed in a subset of cycles that excluded wake predominant intervals. The log-normal mixture model unveils the existence of two separate interval populations (short and long) associated to two different REMep categories (Sequential and Single respectively) among both rats and degus. Single REM sleep episodes are immediately followed by an interlude during which REM sleep transitions are almost absent, that may correspond to a RSRP. The duration of the RSRP increases monotonically in relation to the duration of REMep among rats and degus.

**Concusion:** Rats and degus exhibit a RSRP after Single REMep. The direct relationship between single REMep duration and the following RSRP is consistent with the existence of an hourglass type mechanism regulating the timing of the ultradian sleep cycle among rodents. A post-REM sleep refractory period may be a general property of mammalian sleep architecture.

**Disclosure**: No

## O146/P336 | Investigating the exclusive melanopsin-dependent impact of evening display light on sleep latency, subjective sleep quality and melatonin by silencing cones

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**Objectives/Introduction:** Exposure to evening light from displays elicits changes in sleep and circadian rhythms. These non-image-forming (NIF) effects of light are mediated in part by the photo pigment melanopsin. Melanopsin has a peak wavelength sensitivity of 480 nm at the retinal level, close to the typical 460 nm peak in LED-illuminated displays. Here, we modulated melanopic radiance while keeping cone responses constant (= same visual appearance) to better understand the role of melanopsin signaling on sleep latency, subjective sleep quality, melatonin concentration and melatonin onset.

**Methods:** Seventy-two healthy male participants completed a 2-week study protocol. Volunteers were assigned to one of four groups that differed in luminance levels (27–280 cd/m$^2$). Illuminance while using the display ranged between 7 and 89 lx and were comparable to dim light (Group 1), smartphones (Group 2), tablets (Group 3) or computer screens (Group 4). Each volunteer was exposed to a low melanopic (LM) and high melanopic condition (HM), starting 4 h before habitual bedtime. The LM and HM differed in melanopic irradiance (ca. 3-fold change), but were matched in terms of cone excitation. Polysomnographically assessed sleep latency was manually scored. To evaluate subjective sleep quality, the volunteers completed the Leeds Sleep Evaluation Questionnaire immediately upon awakening from the scheduled 8-h sleep episode. Before, during and after light exposure, salivary melatonin levels were measured in half-hourly intervals throughout scheduled wakefulness.

**Results:** Sleep latency was significantly longer after HM than LM in Group 4 ($p = 0.02$) but not in Groups 1–3. During HM, melatonin concentrations were significantly reduced in all groups compared to LM (Group 1–4: $p < 0.01$, $p = 0.02$, $p < 0.01$, $p < 0.02$). HM delayed melatonin onsets in Groups 1, 3 and 4 ($p < 0.001$, $p = 0.02$, $p = 0.001$). Subjective sleep quality did not yield significant HM vs LM differences.

**Conclusions:** We have first evidence for a selective melanopsin-dependent impact of evening display light prolonging sleep latency and delaying melatonin onset. Furthermore, already low levels of melanopic illuminance elicited NIF effects in the evening. Thus, since many people are exposed to display light in the evening, the selective reduction of melanopsin excitation may potentially reduce unwanted NIF effects of light without compromising visual appearance.

**Disclosure**: No

## O148/P337 | Effects of class start times on social jet lag and associations with academic achievement in university students

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**Introduction:** Class start times impose constraints on sleep-wake behaviour that can result in social jet lag. We used large-scale digital traces of university students (1) to assess the phase resetting effects of class start times on students' diurnal learning behaviour, and (2) to test whether social jet lag was associated with lower grades.
**Methods:** Social jet lag was estimated in 33,645 university students by measuring the phase shift in their Learning Management System (LMS) login rhythm on school days relative to non-school days. We constructed a phase response curve by plotting phase shifts on school days (LMS social jet lag) against the initial phase when students' first class of the day took place. The initial phase was expressed relative to students' LMS login rhythm on non-school days (LMS chronotype). ANCOVA was used to test the association between LMS social jet lag and grade point average, adjusting for demographic variables.
**Results:** Social jet lag was larger in students with a later LMS chronotype and for earlier class start times. The phase response curve revealed that the direction and magnitude of social jet lag were strongly dependent on the phase of students' diurnal rhythm when their first class of the day took place. Phase shifts of up to 12 h were observed when the first class of the day occurred out of phase with students' diurnal rhythm. Students with greater LMS social jet lag had a lower grade point average (ANCOVA: $F_{9,\ 32269} = 44.8$, $p < 0.001$).
**Conclusions:** Class start times had a large impact on students' diurnal behaviour. Students whose diurnal pattern of LMS logins was similar on school days and non-school days obtained better grades than their peers with LMS social jet lag. Universities can potentially improve learning by scheduling classes at times that are better aligned with students' diurnal learning rhythm.
**Support:** Data storage and management were supported by the NUS Office of the Senior Deputy President & Provost and ALSET. The work was funded by the Ministry of Education, Singapore (MOE2019-T2-2-074) and the National Research Foundation, Singapore (NRF2016-SOL002-001).
**Disclosure**: No

## O149/P338 | Regulation of sleep in mice by circadian clock gene *period2*

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**Introduction:** Sleep is regulated by a circadian and a homeostatic process measuring sleep need. Whereas the circadian 24-h oscillation is generated by a set of core clock genes including *Period2* (*Per2*), the molecular substrates underlying sleep homeostasis are unknown. As core clock genes seem to have an additional function as components of the sleep homeostat, our aim was to elucidate the impact of core clock gene *Per2*on the sleep-wake distribution and sleep homeostasis.
**Method:** We used a non-invasive, automatic sleep-scoring piezo system to record sleep/wake behaviour in Per2Brdm mice encoding a mutant PER2protein or lacking *Per2*either completely or cell-specifically, that is, in the neurons or astrocytes specifically. Baseline sleep was measured before mice were subjected to a single 6 h sleep deprivation (SD). Sleep quantity and distribution during baseline sleep and the recovery from SD were analysed. Mice were kept under a 12 h light-12 h dark cycle.
**Results:** During the dark phase control mice show three periods of high wakefulness while mutant *Per2* mice sleep less and show only a bimodal wake distribution (always $n = 9–14$ mice/group; 2-way RM ANOVA). These findings are found to a weaker extent also in mice lacking *Per2*. Female mice of both the mutant *Per2* and the total *Per2* KO mouse strain show an advanced and sustained increase of sleep at the transition from dark to light compared to control females.
Astrocytic Per2 KO females and neuronal Per2 KO males sleep less in 24 h. Except for an absent second high waking period in neuronal *Per2*KO males, sleep distribution is unaltered in mice lacking *Per2* in neurons or astrocytes.
Recovery after SD measured as accumulated minutes of additional sleep is highly variable. Only mutant *Per2* male mice show significantly reduced accumulation of sleep minutes after three days post SD.
**Conclusion:** The circadian clock gene *Per2* influences total sleep time and alters the sleep-wake distribution during the dark phase and at the dark-to-light transition. Astrocytic or neuronal *Per2* does not impact the sleep-wake distribution but reduces sex-specifically the 24 h time-spent-asleep.
**Disclosure**: No

## O150/P339 | Interaction of 14 humans' free-running sleep/wake cycle living in a cave: Is there a social synchronization or not? – deep time mission

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**Introduction:** Light exerts a central role in the entrainment of our 24-h circadian rhythms. In the 1960's, multiple solitary isolation experiments achieved by Michel Siffre and his teams highlighted the endogenous rhythm of the circadian clock, estimated to be around 24.5 h in the absence of any time giver. In our study, the objectives were to determine
(1) whether a group of people living out of time will exhibit the same endogenous rhythm as previously observed and

(2) whether they will synchronize socially or follow their own internal rhythm instead.

**Methods:** Through the Human Adaptation Institute, 14 individuals (7 ♀ and 7 ♂) isolated themselves from any time giver in a cave (Lombrives, France) for a period of 40 days between March and April 2021. Their sleep/wake cycle were monitored by wrist actimetry (Motion Watch, CamNTech) for 3 days before entering the cave ("Pre"), during the 40 days in the cave ("Per") and 14 days after exiting the cave ("Post"). A sleep diary was completed each cycle.

**Results:** Within the 40 days, we recorded 24 to 31 sleep/wake cycles per subject (mean ± sd: 29.25 ± 2.56) with a mean duration of 31.7 h ± 8.0 per cycle. No sex differences were observed. The ratio "time awake" to "time asleep" stayed stable across all conditions ("Pre": 64.63% ± 5.9, "Per": 63.64% ± 8.78 and "Post": 62.36% ± 8.27, $p = 0.201$). After a period lengthening and a regular phase delay observed within the group during the first week, great irregularities from one cycle to another started and lasted until the end of the experiment for all subjects respectively. Analysis of circadian markers (melatonin, cortisol, temperature) is underway to confirm these results.

**Conclusion:** We show for the first time that subjects prefer to follow their own internal rhythm over following a social synchronization when isolated from external time giver and free of any constraints. Interestingly, the ratio rest/activity stay the same in and outside the cave, even though their internal rhythms tend to be longer than what were previously shown by other studies, leaving a field open to other hypotheses concerning human adaptations.

**Disclosure**: No

## O151/P340 | Resetting of the circadian rhythm of melatonin by exposure to moderate hypoxia in humans

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**Objectives/introduction:** Research in rodents revealed daily rhythms in tissue oxygen levels and indicated that modulation of oxygen levels–via activation of hypoxia inducible factor 1α (HIF-1α)–may be a resetting cue for circadian clocks. Understanding the link between circadian and hypoxia-sensing pathways may provide insight into novel therapies for jet lag and other circadian disorders. We studied the effects of late-evening exposure to moderate hypoxia on the circadian melatonin rhythm in humans.

**Methods:** Twenty-two healthy adults (12 women; mean age ± SD: 25.2 ± 2.7 years) participated in a randomised, single blind, crossover study. Participants followed a fixed 8-h sleep schedule prior to and during two 4-day laboratory visits during each of which the circadian rhythm of melatonin was measured twice, once before and once after treatment. During treatment, oxygen concentration in the atmosphere was lowered to 15% for 6.5 h, centred at 23:00 h (hypoxia; corresponding to an altitude of 2438 m), or no change in oxygen was applied (control). Dim light melatonin onset (DLMO) was derived on days before and after treatment through hourly blood sampling in constant posture. The shift in DLMO was compared between the hypoxia and control condition. Blood oxygenation was measured with a finger pulse oximeter throughout the night of exposure. Transcription of HIF1α and target genes was determined in whole blood samples before and during hypoxic exposure.

**Results:** Exposure to hypoxia lowered blood oxygenation such that values were lowest during the interval that overlapped with the sleep episode (23:00–02:15 h; mean, 95% CI: 86.4, 85.2%–87.7%). Late-evening hypoxia exposure induced a phase advance of DLMO (mean, 95% CI: 8.6, 0.9–16.3 min; $n = 21$; $p < 0.020$, Wilcoxon; corrected for circadian drift during control). No changes were observed in HIF-1α related transcription.

**Conclusions:** Exposure to hypoxia may work as a zeitgeber of the central circadian clock in humans. This effect does not appear to be mediated through changes at the level of HIF-1α transcription. While the observed phase-shifting effect of hypoxia was small, its magnitude is such that circadian entrainment to a 24-h cycle appears to be possible.

**Disclosures:** Nothing to declare. Research was funded through the Aeronautics Program of the German Aerospace Centre.

**Disclosure**: No

## O152/P341 | Relaxation of social time pressure promotes co-alignment of daily fasting and sleep cycles

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**Objectives/Introduction:** Sleep regulation in humans is tightly linked to social time pressure (STP) that assigns local time to meals, work, family time, and additional daily activities. The impact of the STP decrease on daily rest-activity cycles during COVID-19-mandated social restrictions (SR) has been studied epidemiologically by our and other research groups. These studies consistently showed that nocturnal sleep duration (SD) increased, social jetlag (SJL) decreased, and mid-sleep times on free days (MST, a proxy for chronotype) delayed during SRs. Here, we investigated in the Global Chrono Corona Survey (GCCS) dataset changes in the interrelationships between the temporal organization of daily sleep-wake and fasting parameters under regular, strict (before the SRs) and relaxed (during SR) STP in the general population.

**Methods:** The GCCS was conducted during the first wave of SRs between April 4 and May 6, 2020 in 40 countries. The final sample consisted of 7,517 respondents (68.2% females), who did not contract COVID-19 virus, and had been on average 32.7 ± 9.1 days under SRs. Daily eating patterns were quantified in terms of fasting duration from the last to the first meal (FD) and its timing represented by the mid-fasting time (MFT). To assess the magnitude of fasting and sleep cycles (mis)alignment, we introduced two new factors: the difference in fasting and sleep duration (ΔFDSD) and the difference between the two midpoints (ΔMFMS).

**Results:** Before SRs, sleep and fasting parameters showed multiple robust correlations, both in their timing ($\rho = 0.45$), and their duration ($\rho = 0.25$). ΔMFMS correlated negatively with MST (chronotype), indicating that the later chronotype the larger fasting-sleep misalignment. ΔMFMS correlated also with the SJL ($\rho = -0.47$). During SRs, FD became longer by 41 min, mainly driven by later breakfast times. SD increased on average by 15 min. Mean ΔFDSD increased by 15 min, while ΔMFMS remained unchanged. The correlation between MST and MFT was substantially strengthened ($\rho = 0.65$); MST became correlated with FD ($\rho = 0.21$).

**Conclusions:** During weeks-long reduced social time pressure, induced by social restrictions, sleep and fasting parameters became more tightly linked. Relaxed STP may promote co-alignment of daily fasting and sleep cycles and benefit overall health.

**Disclosure**: No

### O153/P342 | Comparative sleep analysis of C3H/HeN and C57BL/6 mouse strains

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The C57bl/6 mouse strain, although commonly used in sleep and circadian rhythm research, is a strain lacking a melatonin rhythm and exhibiting very low levels of pineal and plasma melatonin. In contrast, C3H/HeN mice do show a clear melatonin rhythm. Because of the implied role of melatonin in sleep and circadian rhythms, we compared sleep parameters of male C57bl/6 ($n = 5$) and C3H/HeN ($n = 7$) mice. We analysed 10-day locomotor activity, and recorded electroencephalogram (EEG) brain activity to analyse vigilance state distribution and changes in brain activity over a 24-h baseline, subsequent 6-h sleep deprivation (starting at lights on), and 18-h recovery period.

Activity profile analysis indicated a gradual decrease of locomotor activity in the course of the active phase for C3H/HeN, while C57bl/6 showed multiple peaks. C3H/HeN and C57bl/6 spent the same time awake in the light (246 vs 265 min, respectively, *T*-test, $p = 0{,}118$) and dark phase (479 vs 533 min, *T*-test, $p = 0{,}432$). C3H/HeN spent the same amount of time in rapid eye movement (REM) sleep in the light phase (76,1 vs 66,9 min, $p = 0{,}218$), but showed more REM-sleep in the dark (36,7 vs 13,8 min, *T*-test, $p = 0{,}002$). C3H/HeN spent remarkable little time awake during ZT23-24 (15,9 vs 51,6 min/h, *T*-test after GLM with significant factor strain × time, $p = 0{,}005$). C3H/HeN displayed higher absolute EEG activity between 5–7 Hz (*T*-test $p < 0{,}005$) across all stages and showed a stronger daily modulation of EEG power density than C57bl/6 across almost the entire spectrum (0–25 Hz) in NREM-sleep (*T*-test for amplitude of fitted sine waves, $p < 0{,}0041$). After sleep deprivation C3H/HeN showed a larger increase in slow wave activity (0,5–4 Hz) relative to baseline (GLM for factor strain × time $p < 0{,}001$).

The comparison between C3H/HeN and C57Bl/6 mice reveals several differences in vigilance state timing and EEG activity between the strains, as well as a rhythmic component in EEG power density stronger in C3H/HeN compared to C57bl/6. It is possible that some of the differences observed, like the daily rhythm in EEG power density, are explained by the presence of a melatonin rhythm. However, beyond melatonin, there are several other differences between the two strains that might underlie the dissimilarities observed.

**Disclosure**: No

## 7: PHYLOGENETIC AND EVOLUTIONARY STUDIES

### O099/P343 | Changes in reindeer sleep regulation across the year: a central role for rumination?

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**Objectives/Introduction:** Most non-hibernating animals maintain daily "circadian" rhythms of sleep across the year, as well as "homeostatic" sleep-wake patterns in which increasing time awake is followed by increased sleep amount or intensity. Strikingly, ruminant reindeer in the Arctic show 24-h rhythmicity at the equinoxes, but none at either solstice; and summertime activity greatly exceeds wintertime activity. So far, though, nothing is known about their sleep or how it might be seasonally modulated.

**Methods:** We simultaneously recorded non-invasive electroencephalography (EEG) in four adult, female reindeer (Rangifer tarandus tarandus) for four days at The Arctic University of Norway in Tromsø (Norway) in July, September, and December. Rapid eye movement (REM) sleep, non-REM (NREM) sleep, and rumination were visually identified from the EEG and slow-wave activity (SWA, EEG power 1–

4.5 Hz) during NREM sleep, the classic marker for homeostatic changes in sleep pressure, was calculated.

**Results:** Although sleep in reindeer generally resembled that of other mammals, key novel adaptations were observed (July/September: $n = 4$, December: $n = 3$). Similar to most species, sleep-wake distribution paralleled daily activity during seasonally changing light-dark conditions and SWA during NREM sleep was increased after prolonged wake periods ($t = 5.9$, $p < 0.01$). Surprisingly, total sleep duration was roughly equal across seasons, and prolonged waking produced a lower SWA response in summer than winter ($t = -2.54$, $p = 0.02$). As reported for some domestic ruminants, EEG during rumination showed typical characteristics of NREM sleep. Furthermore, rumination appeared to be able to substitute for sleep under all conditions observed. Accordingly, SWA decreased across rumination ($t = 4.4$, $p < 0.01$) and total rumination and NREM sleep durations were negatively correlated ($r = -0.63$, $p = 0.04$). Homeostatic modelling of SWA further suggested that rumination was equivalent to sleep.

**Conclusions:** We suggest that less pronounced SWA increases across waking in summer might indicate higher baseline sleep pressure during this season, possibly resulting from increased activity, food intake and light exposure. Within this context, rumination might act as a partial substitute for conventional sleep, permitting near-constant feeding in the arctic summer while compensating for increased sleep pressure.

**Disclosure**: No

## 8: BEHAVIOUR

### O091/P352 | Local slow-wave activity in regular sleep is associated with individual risk preferences

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**Objectives/Introduction:** Risky behaviours can have enormous health and economic consequences and the propensity to engage in risky decisions greatly differs between individuals. Previous research has shown that manipulation of sleep affects risky decision-making. However, it yet remains to be understood how individual temporally stable neural sleep characteristics in regular, healthy sleep relate to individual differences in risk preferences.

**Methods:** Using a portable high-density polysomnographic system, we collected sleep electroencephalographic (EEG) data in 54 healthy young adults at participants' home without experimenter's supervision (21.11 ± 2.04 years, 42 females). Slow-wave activity (SWA; spectral power 0.8–4.6 Hz) was computed in sleep stages N2 and N3. Before statistical analysis, individual SWA distribution maps were normalized to the mean values across all electrodes to reduce confounds without regional specificity. Risk preferences were assessed using a newly developed task in the behavioural laboratory.

**Results:** Participants showed large inter-individual variability in risk preferences (mean 16.48, SD = 9.7, range: 0–40). Regression analyses revealed that lower local sleep depth, as reflected by SWA in a cluster of electrodes located over the right prefrontal cortex (PFC) is associated with higher individual risk preferences (rho(52) = −0.38, $p = 0.004$, $R^2 = 0.14$, cluster based corrected for multiple testing). Importantly, controlling for total sleep time or time spent in deep sleep, that is, stages N2 and N3 did not affect this result (rho(51) = −0.39, $p = 0.004$, $R^2 = 0.15$; rho(51) = −0.39, $p = 0.004$, $R^2 = 0.15$). Moreover, the association between SWA over the right prefrontal cortex and risk preferences was evident across all sleep cycles.

**Conclusion:** Our findings show that local sleep depth in the right PFC has a significant impact on risk preferences. The right PFC is an area involved in cognitive control functions. Hence, we speculate that local sleep depth in the right PFC might serve as a dispositional indicator of impulse control ability, which is expressed in risk preferences.

**Disclosure**: No

## 9: LEARNING, MEMORY AND COGNITION

### O088/P367 | Uncoupling of stimulus processing and memory encoding during the wake-sleep transition

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**Introduction:** The transition from wakefulness to sleep is marked by a loss of our ability to perceive, store and respond to external information. However, there is no single time point clearly defining sleep onset. The current study investigates differences in the disintegration of different information processing components during the wake-sleep transition.

**Methods:** 19 participants (9 female) were instructed to fall asleep while listening to an audiobook and simultaneously react to a tone by pressing a key. After a 90-minute sleep cycle, participants were awoken and had to perform free recall of the audiobook content and a recognition task for different passages of the audiobook rating their memory confidence. This procedure was repeated up to 5 times per

night resulting in 78 wake-sleep transitions. Electroencephalography (EEG) was recorded during the whole night and sleep scoring was performed by two independent raters. Tone responsiveness (proportion of responses of the total number of tone presentations) was calculated separately for each sleep stage. Frequencies of last responses to the tone and last memory of audiobook content were counted for each sleep stage and the distribution of frequencies across sleep stages were compared in a chi-square test.

**Results:** Tone responsiveness of the participants was 100% during wakefulness, 90% during sleep stage 1, and 68% during sleep stage 2. In 64% of transitions, the participants' last response occurred in sleep stage 2 or deeper. The last time point during which participants retrospectively recognized audiobook content fell within the stage of wakefulness in 56% of transitions, sleep stage 1 in 40% of transitions, and later stages in 4% of transitions. The frequency distribution of last tone responses and last audiobook memory show a significant difference between sleep stages ($\chi^2 = 85.83$, $p < 0.001$).

**Conclusions:** In the transition to sleep, participants' ability to encode the content of an audiobook ceased earlier than their ability to respond to a tone. This indicates a disintegration of different information processing components, with more complex cognitive processes breaking down prior to more basic cognitive processes like simple stimulus responses. These findings support the idea of the process of falling asleep being a multifaceted process.

**Disclosure**: No

## O089/P368 | Neural correlates of phase-dependant motor memory consolidation: a multimodal study

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**Introduction:** Motor memory consolidation can be enhanced by targeted memory reactivation (TMR) during post-learning sleep. Based on evidence that brain excitability fluctuates with the phase of sleep oscillations such as Slow Waves (SW), we hypothesized that the effect of TMR on memory consolidation depends on the phase of the stimulated SW. In this study, we employed a sophisticated, closed-loop stimulation procedure to apply TMR at two different phases of the SW (up vs. down) and tested the effect of these phase-specific stimulations on the behavioural and neural correlates of motor memory consolidation.

**Methods:** Thirty-one healthy participants (age range: 18–30) participated in this study. Each participant was scanned with fMRI while performing a motor sequence learning (MSL) task including three different movement sequences (associated to three different sounds) before and after a night of sleep monitored with EEG. Two sequences were reactivated during post-learning sleep (the third sequence served as a no reactivation condition) at different phases of the SW (up vs. down) using real-time SW detection and closed-loop auditory stimulation procedures.

**Results:** Behavioural data revealed that TMR time-locked to the SW-down phase resulted in deterioration of performance as compared to up and no stimulation ($p = 0.034$). EEG data revealed phase-specific modulations of SW amplitude at the peak of the SW, whereby up-stimulated SWs showed higher amplitude ($p = 0.002$). Time-frequency analyses revealed that sigma band power was significantly higher for the up- than the down-stimulated SWs during the ascending phase of the SW ($p = 0.008$). Brain imaging data indicated that striatal activity increased from training to the overnight retest more in the up as compared to the down and not-reactivated conditions (p-unc < 0.002). Hippocampal activity decreased overnight more in the not-reactivated condition than in the up condition (p-unc = 0.001).

**Conclusion:** At the behavioural level, our results indicate that TMR effects depend on the phase of the stimulated slow oscillation. At the brain level, our data provide strong evidence for a phase-dependent effect of TMR on the modulation of SW amplitude and sigma power as well as of task-related activity in the striatum and the hippocampus, i.e., brain waves and regions critically involved in motor memory consolidation.

**Disclosure**: No

## O090/P369 | Sleep effects on multi element events

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**Introduction:** Sleep is known to benefit the consolidation of previously encoded simple associations. However, in real life, events often have a more complex structure. In the present study, we therefore investigated if and to which extend sleep benefits the consolidation of multiple interdependent elements of strong, weak, and not directly encoded associations.

**Methods:** Fourteen healthy human participants engaged in a word-pair learning task consisting of events that included four different elements and that were encoded in a specific pattern to foster formation of either strong or weak associations between the elements. Following an immediate recall, participants either slept (Sleep condition) or stayed awake (Wake condition) at night. On the third day, following

an additional night at home (which served as recovery night in the Wake condition), participants returned to the laboratory for a delayed recall. Participants were tested on their retrieval performance of strongly and weakly encoded associations. In addition, we tested their ability to recall pairs of words that have not been encoded directly (nonencoded associations) but could be inferred from the encoded material.

**Results:** Sleep, compared to wakefulness, improved memory retention for weak ($p = 0.002$) but not for strong associations ($p = 0.771$), and also strengthened participants' knowledge of nonencoded associations ($p = 0.034$). In addition, after sleep vs. wakefulness, we found a stronger dependency between associations of the four-element events (i.e., the probability to retrieve two elements of the same event given a single common cue word; $p = 0.036$). Analyses of variance (ANOVA) including the repeated-measures factors Sleep/Wake and Pre/Post (i.e., before vs. after the sleep/wake manipulation) were used for statistical comparisons ($n = 14$ participants).

**Conclusions:** Our findings support the notion that sleep benefits memories depending on the strength of encoding. In addition, our results suggest that sleep is beneficial for inferring information that has not been encoded directly. Finally, our findings suggest a beneficial effect of sleep on "pattern completion", that is, a fundamental capability of the brain, specifically the hippocampus, to recall all elements of an event based on a partial cue.

**Disclosure**: No

## O092/P370 | Selective reactivation of memories during sleep impairs non-reactivated memories in the same context

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**Objectives/Introduction:** Targeted memory reactivation (TMR) benefits consolidation and remembrance of the reactivated memories. However, it is unclear whether and how much improvement of the targeted memories affects the performance of non-targeted memories. Here, we tested if TMR prioritizes activated memories at the cost of remembering related but non-activated memories within the same context.

**Methods:** In **study-1**, twenty healthy males (M ± SD, 22.45 ± 2.78 yrs., range, 19–30) underwent three experimental sessions in a randomized order (sleep/wake/sleep-control). During sleep/wake-session, participants encoded two word lists with a mnemonic strategy (method of loci), which binds each list into a related set. Auditory cues for half of the words from one list were presented again at 45dB during slow-wave sleep (SWS). Two-memory tests were performed after learning immediately/90-mins in the fMRI scanner. Participants were able to take a 60–70 min nap(sleep) or watch a non-arousing movie(wake) between two-test intervals. Eleven subjects fulfilled all criteria for further analysis.

**Study-2**, will perform a 3-h overnight preregistered replication of study-1 with thirty participants. Subjects will undergo four experimental sessions in a randomized order (strategy-learning/sleep-adaptation/sleep/wake-control). Participants will learn four-word lists, of which half of the words of two lists and twenty words not from the four word lists associated with an auditory cue will be presented during sleep. The post-memory test will be performed immediately and three days later.

**Results:** In study-1, a significant sleep effect on memory recall was found between the sleep (post/pre: 102.3% ± 3.8%) and wake (post/pre: 99.1% ± 1.9%) sessions ($t(10) = 2.153$, $p = 0.029$); the cued vs. un-cued items of the cued word list ($t(10) = 1.837$, $p = 0.048$). In contrast, the cued vs. un-cued word list as a whole ($t(10) = 0.767$, $p = 0.231$) did not differ significantly in later recall, with a benefit for the cued and a performance decrease for the un-cued words. Preliminary fMRI results showed significant activation differences in the right Para hippocampal gyrus and left inferior parietal lobule (cluster-level corrected $p < 0.05$) for cued versus un-cued items of the cued word list.

**Conclusions:** TMR during sleep can benefit the remembrance of targeted memories but at the cost of remembering the non-targeted memories within the same context. These findings suggest possible directions for opening new treatment modalities for mood disorders.

**Disclosure**: No

## O093/P371 | Time- and induction- but not sleep-dependent modulation of resting-state fast brain dynamics in motor learning and consolidation

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In motor learning (ML), performance rapidly improves during practice, then spontaneously evolves further offline ~30 min after the end of practice (boost period) to be back to end-of-learning levels after ~4 h (silent period) and improve again after a sleeping night. Hidden Markov modelling (HMM) of magnetoencephalographic (MEG) power envelope during the resting-state (RS) highlights fast transient, sub-second variations in brain networks, allowing to investigate the neural

plasticity dynamics underlying ML and its consolidation. Using HMM, we investigated the impact of diurnal post-training sleep (nap vs. wake) followed by a night of sleep on neural activity dynamics within ML-related cerebral networks.

**Methods:** Young healthy participants were trained on a Finger Tapping Task (FTT; 20 blocks), then were tested (FTT; 2 blocks) after 20 min, 4 h, and the next morning. Half of the participants ($N = 15$) had a 90-min nap 2 h after learning; another half ($N = 12$) stayed awake. Five-minute MEG (306-channels Triux, MEGIN) RS recordings were obtained (a) before learning and (b) both before and after each testing session (20 min, 4 h, next day) to differentiate motor practice-induced (post-testing) from non-induced (pre-testing) brain activity.

**Results:** HMM highlighted 8 recurrent topographical brain states. Repeated measures ANOVA were conducted on 4 temporal parameters (mean life time, MLT; fractional occupancy, FO; mean interval length, MIL; number of occurrences, NO) with within-subject factors Session (20 min, 4 h, 24 h) and Induction (pre- vs. post-testing) and between-subject factor Group (nap vs. wake). Results disclosed main Session effects ($ps < 0.05$) for most temporal parameters in topographical states 2 (Sensorimotor/Cuneus), 6 (Angular), and 8 (Somatosensory), with marked overnight changes, as well as main Induction effects in most states ($ps < 0.02$). Nap-related effects were non-significant.

**Conclusion:** Preliminary results indicate time-dependent modulation of ML-related neural networks, with marked changes observed after a 24 h-delay with a night of sleep, however not modulated by the opportunity of post-training sleep (nap). Induction-related HMM changes show that even a short testing period modulates RS activity in ML-related neural networks.

**Disclosure**: No

## O172/P660 | Time- but not sleep-dependent remodelling in brain microstructural components after motor sequence learning: A diffusion-weighted imaging study

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**Introduction:** Diffusion-weighted imaging (DWI) allows the observation of (micro) structural brain remodelling after restricted motor learning time. Although sensitive, diffusion tensor imaging (DTI) is unspecific about underlying cellular processes. Multicompartment Neurite Orientation Dispersion and Density Imaging (NODDI) estimates dendritic and axonal microstructural complexity and allows tracking with improved specificity neural density changes developing in the short-term. Post-learning sleep could result in long-term microstructural brain changes, but concrete evidence remains scarce. Here, we used DTI and NODDI to investigate the microstructural brain mechanisms underlying time- and sleep-dependent motor memory consolidation.

**Methods:** Sixty young (18–30y) healthy adults underwent baseline magnetic resonance DWI(1) then trained on a 1 h-Serial Reaction Time Task (SRTT; 30 blocks – 96 trials/block) followed by DWI (2) (Day1). They slept or stayed awake the next night, then slept 3 nights at home. On Day 5, they underwent DWI(3) before being retrained on SRTT (40 min; 20 blocks), then DWI(4). DTI/NODDI analyses were conducted on 6 bilateral subcortical regions of interest (ROIs).

**Results:** A multivariate analysis on DTI/NODDI parameters revealed short-term microstructural modifications following learning/relearning in left thalamus, bilateral putamen, hippocampus, and cerebellum ($ps < 0.001$) and right putamen ($p = 0.008$). Univariate post-hoc tests disclosed (a) decreased mean diffusivity (MD) in bilateral putamen, hippocampus, and cerebellum, (b) increased neurite dispersion index (NDI) in left hippocampus and bilateral putamen, and (c) decreased free water fraction (FWF) in left thalamus and cerebellum. Delayed learning-related changes ($p = 0.007$) were found in left putamen with (a) increased fractional anisotropy (FA) and (b) decreased orientation dispersion index (ODI) on Day 5. No sleep-related effects were significant ($0.020 < ps < 0.853$).

**Conclusions:** MD reductions in subcortical ROIs after motor practice confirm previously reported motor learning-related microstructural changes developing in the short term. Reduced FWF in similar regions indicates increased tissue proportion following learning, whereas enhanced NDI in left thalamus and cerebellum suggests a rapid motor learning-related reorganization in brain tissue microstructure and neurite density. Fibers in left putamen showed a higher directionality reflected by both FA and ODI changes, probably capturing longer-term structural brain plasticity. However, post-training sleep manipulation did not seem to impact learning-related microstructural changes.

**Disclosure**: No

## O187/P661 | Fast spindle clustering declines with age and shows opposite associations with memory consolidation and NREM sleep fragmentation

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**Objectives/Introduction:** Recent studies in rodents and in young adults have shown that fast spindle band power fluctuates at a 0.02-Hz infra-slow scale during NREM sleep. These fluctuations result from a periodic clustering of spindles and are thought to modulate sleep maintenance and the efficiency of memory consolidation. However, these dynamic aspects of NREM sleep have not been investigated so far in older adults. Our objectives were to compare fast spindle band power fluctuations in young and older adults and to better characterize fast spindle clustering (impact of age, effects on spindle features, links with memory consolidation and sleep fragmentation).

**Methods:** A polysomnography was performed in 147 older adults (mean age ± SD: 69.3 ± 4.1 y), among which 134 were included in the Age-Well RCT, and 32 young-middle aged adults (34.5 ± 10.9 y). A subsample of 57 older participants performed a visuospatial memory task before and after polysomnography. We analyzed power fluctuations in fast spindle frequency band during NREM sleep, detected fast spindles and quantified their clustering level using Boutin & Doyon (2020) criteria. The relationship between age and the proportion of clustered fast spindle was tested using linear and non-linear models. Linear mixed models were used to evaluate the effect of clustering level on spindle characteristics. Linear regressions were also performed to test the associations of fast spindles with memory consolidation and NREM sleep micro-arousals, controlling for age and sex.

**Results:** Fast spindle band power fluctuated at the same 0.02-Hz infra-slow scale in both groups. However, the proportion of clustered fast spindles decreased non-linearly with age, dropping after 50 years ($p < 0.001$). The clustering level of fast spindles modulated their characteristics, such that fast spindles in long clusters exhibited increased amplitude and duration compared to isolated fast spindles (all $p < 0.001$). Finally, the mean number of fast spindles per cluster was positively associated with memory consolidation ($p < 0.05$) and negatively associated with the density of NREM sleep micro-arousals ($p < 0.05$).

**Conclusions:** Clusters of fast spindles could constitute periods of stable sleep promoting memory consolidation. The reduction of fast spindle clustering with age could contribute to increase sleep fragmentation and impair sleep-dependent memory consolidation.

**Disclosure**: No

O238/P662 | **Boosting sleep improves motor learning in mice**

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**Introduction:** The benefits of a good night of sleep on motor learning are well established in humans, while in animals this evidence is more elusive. Recent work has shown that loss of sleep significantly impacts mouse motor performance when a complex motor sequence is carried out. Indeed, sleep deprived mice performed worse on the complex wheel task, which requires mice to learn how to adapt their running on a wheel with irregularly spaced rungs. This finding prompted us to hypothesise that sleep enhancement, on the contrary, could improve motor performance on this very task.

**Methods:** We took advantage of a recent discovery showing that NREM sleep can be extended in mice by gently rocking them with an orbital shaker. Thus, C57BL/6 male mice (postnatal day 45) were divided in normal sleep (S, $n = 12$) and sleep enhancement (SE, $n = 15$) groups. S mice were left undisturbed, while SE mice were rocked at 1 Hz for 12 h/day during the light period for 11 consecutive days. During this period, all mice had access to a complex wheel for 12 h/day during the dark period. Food and water were available ad libitum. Mouse motion activity was continuously detected with an infrared camera and used as a proxy of sleep and wake behaviour. Motor learning was calculated as the ratio between final (day 11) and initial (day 1) maximum and average speed.

**Results:** We found that SE mice slept longer throughout the experiment with a daily increase of inactivity time relative to S that ranged from 2.05% to 9.04% ($p = 0.02$). SE also showed average lower number of sleep to wake transitions indicative of more consolidated sleep ($p < 0.001$). Finally, SE group showed improved learning relative to S group ($p = 0.042$ for average speed, $p = 0.016$ for maximum speed), and the extent of learning was correlated with the amount of sleep in both S and SE mice ($r = 0.6$ $p = 0.0011$ for average speed; $r = 0.59$ $p = 0.0011$ for maximum speed).

**Conclusions:** Sleep enhancement via rocking increases mouse motor learning performance at the complex wheel task, suggesting that vestibular stimulation during sleep could be a viable way to improve cognition.

**Disclosure**: No

## 11: SLEEP DEPRIVATION

O169/P672 | **A1 adenosine receptor availability under chronic sleep restriction and its association with cognitive performance**

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**Objectives:** Studies on total sleep deprivation have linked the individual vulnerability to sleep-loss induced performance impairments to

the cerebral adenosinergic regulation. Here we aimed at investigating the impact of chronic sleep restriction on this system.

**Methods:** Thirty-six volunteers followed a protocol of 3 baseline nights (8 h time in bed, TIB), 5 experimental nights, and one recovery night (8 h TIB). The sleep restriction group ($N = 21$) had 5 h TIB during experimental nights, while the control group ($N = 15$) had 8 h TIB. We quantified A1 adenosine receptor (A1AR) availability with [18F]CPFPX positron emission tomography at experimental day 5 (ED5) and at the recovery day (REC). Median reaction time (median RT) and 10$^{th}$ percentile of reaction time (10P RT) in a 10-min Psychomotor Vigilance Task were analysed at baseline day 3 (BL3), ED5, and REC. We used mixed ANOVAs with Tukey adjusted post-hoc comparisons for analyses. We correlated the change in A1AR availability (ED5 minus REC) with the change in performance.

**Results:** A1AR availability neither differed between the sleep restriction group and the well-rested control group (both at ED5 and REC), nor within the sleep restriction group comparing ED5 and REC (all $p > 0.35$). In the sleep restriction group, performance was impaired at ED5 and REC in comparison to BL ($p < 0.02$), and did not differ between ED5 and REC ($p > 0.7$). However, the individual change in A1AR availability was correlated with the change in performance (Median RT: $r = 0.46$, $p = 0.06$; 10P RT: $r = 0.54$, $p = 0.03$) such that faster RTs at REC compared to ED5 were associated with increased A1AR availability and vice versa.

**Conclusions:** Even though performance was impaired by sleep restriction and remained impaired after recovery, A1AR availability was unchanged by sleep restriction. This contrasts with findings from total sleep deprivation in which we found impaired performance and increased A1AR availability after 52 h of wakefulness that were both restored to rested levels after recovery sleep. The findings reveal fundamental differences in the mechanisms through which total and chronic sleep loss affect adenosinergic regulation and cognitive performance.

**Disclosure**: No

## O170/P673 | Reversal learning and working memory scanning task performance improve with bright light exposure during simulated night work: a counterbalanced crossover study

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**Objectives/Introduction:** Night work leads to reduced alertness and vigilance during work h, especially in the later parts of the night shift. Bright light interventions have the potential to reduce such effects. Against that backdrop we aimed to investigate whether a bright light intervention, compared to a standard light condition, improved reversal learning and working memory scanning task performance during simulated night work.

**Methods:** Healthy young university students were screened (e.g., normal sleep, no relevant diseases/disorders, not extreme chronotypes), recruited and enrolled into a counterbalanced crossover study where they twice performed three consecutive simulated night shifts in a laboratory. About half of the participants started with night shifts in a full-spectrum (4000 K) bright light condition (vertical illuminance: ~900 lx, irradiance: ~270 μW/cm$^2$), while the other half started with a standard light condition (vertical illuminance: ~90 lx, irradiance: ~27 μW/cm$^2$). After a 4-week washout period, the participants completed the second study bout with the opposite light condition. During the night shifts, a working memory scanning task and a reversal learning task were administered in the early parts of the night shift (session 1, 00:10 h), and again in the later parts of the night shift (session 2, 04:40 h).

**Results:** Twenty-six participants (20 females, 19–27 years of age) were included in the analyses. Linear Mixed Model (LMM) analyses indicated that with the bright light condition, compared to the standard light condition, the participants' reversal learning performance in terms of discriminability (i.e., ability to discriminate between go and no-go stimuli in the task) was improved in session 2 (04:40 h). In session 1 (00:10 h) participants performed equivalently in both light conditions. Similarly, for the working memory scanning task, LMMs indicated that performance (i.e., accuracy) was improved in session 2 with the bright light condition, compared to the standard light condition.

**Conclusions:** This study suggests that bright light interventions may be beneficial for night workers' performance on tasks that require cognitive flexibility and control (e.g., reversal learning tasks). Such elements of cognition are considered particularly relevant for real-life settings where the ability to adapt to changes in the environment is important.

**Disclosure**: No

## O171/P674 | Does repeated coffee consumption during chronic sleep restriction affect $A_1$ adenosine receptor availability in humans?

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**Objectives:** Adenosine and cerebral adenosine $A_1$ ($A_1$AR) and $A_{2A}$ receptors are important modulators of the sleep-wake cycle and regulate to some extent the sleep-wake homeostasis. Acute sleep deprivation has been shown to result in an upregulation of $A_1$ARs in human and rat brains. The stimulating effects of caffeine are evoked through non-selective antagonism at adenosine receptors. Using positron emission tomography (PET), we investigate the effect of repeated coffee consumption during chronic sleep restriction and subsequent coffee abstinence after recovery sleep on cerebral $A_1$AR availability and occupancy in humans.

**Methods:** Thirty healthy volunteers (28 ± 5 years, 15f) completed an in-lab study including three [$^{18}$F]CPFPX PET scans to determine cerebral $A_1$AR availability after subsequent exposure to rested (3 nights with 8 h time in bed [TIB]), chronically sleep restricted (5 nights with 5 h TIB), and recovery (one night with 8 h TIB) conditions. Participants either consumed freshly brewed coffee ($n = 17$) or decaffeinated coffee ($n = 13$) during 5 days of sleep restriction (prior caffeine abstinence > 10 days). Regular coffee contained 200 mg caffeine at 7:30 a.m. and 100 mg caffeine at 2:00 p.m., decaffeinated coffee contained 4 mg and 2 mg, respectively. PET scans were conducted at the same time of day under caffeine-abstinent rested conditions, roughly 7 h after the latest coffee intake after sleep restriction, and after~31 h of coffee abstention after recovery. Caffeine levels in saliva were determined repeatedly. Cerebral $A_1$AR availability was quantified by distribution volume ($V_T$) and occupancy levels were calculated by applying the Lassen plot including cortical and subcortical areas, cerebellum and pons.

**Results:** In the decaffeinated coffee group, no differences in cerebral $A_1$AR availability were found between baseline condition, 5 days of sleep restriction and one night of recovery sleep. Repeated administration of regular coffee resulted in a displacement of [$^{18}$F]CPFPX binding of 19 ± 13% on average. One day after coffee abstention and recovery sleep, $V_T$ values did not differ from baseline.

**Conclusions:** Our data suggest that neither chronic sleep restriction for 5 days nor combination with repeated caffeine consumption result in a persistent change in the regulation of cerebral $A_1$AR availability.

**Disclosure**: Yes

**Conflict of Interest statement: Financial support:**
The work was supported by the Institute for Scientific Information on Coffee, the Swiss National Science Foundation (# 320030_163439) and respective institutional funds.

## O173/P675 | Compensating effects of operator fatigue due to sleep loss through collaborative team work in a control room situation

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**Objectives/Introduction:** Sleep deprivation is associated with impaired individual cognitive performance. Although team performance is also widely common in occupational settings requiring adverse working times, research on the effects of fatigue on team performance is scarce. We investigated how sleep deprivation affects team performance in a simulated control room expecting that operators' performance is less deteriorated by fatigue when collaborating in a cooperative team than when working alone.

**Methods:** Sixty-six healthy volunteers (32 females, mean age ± SD: 26 ± 5 years) were randomly assigned to small groups of 3 members and underwent a sleep laboratory study for 5 consecutive days. Each participant performed a simulated control room task including a monitoring task (monitoring for system failures requiring sustained attention) and a diagnosis task (identifying the cause of system failures by logical reasoning) once during daytime after 1 h of wakefulness (baseline), and once during the circadian low after 19 h of wakefulness (sleep deprivation). Three team conditions (solo, i.e., working alone, cooperative team, competitive team) were applied.

**Results:** In the monitoring task, mixed-model analysis showed slower reaction times and less accuracy under sleep deprivation than during baseline (both $p < 0.001$), and faster responses, but less accuracy in the solo condition than in both team conditions (both $p < 0.001$). There was no interaction between sleep and team condition for both performance indicators. In the diagnosis task, participants were slower when sleep deprived compared to baseline ($p < 0.001$), and in both team conditions compared to solo (both, $p < 0.001$). There was a significant interaction effect between sleep and cooperative team condition for accuracy ($p < 0.001$), but not for the competitive team condition and not for speed. In contrast to solo work participants in the cooperative team condition were even more accurate under sleep deprivation than during baseline.

**Conclusions:** Sleep deprivation combined with an adverse time of day affects not only individual performance, but also team performance in a control room simulation. Though team work was associated with longer response times than solo work, working collaboratively on a task appears to protect against some effects of fatigue on logical reasoning.

**Disclosure**: No

## O174/P676 | No sleep makes your brain look older: sleep deprivation increases brain age in humans

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**Objectives:** Sleep is fundamental for the maintenance of physical and psychological functions. Specifically, sleep loss and sleep restriction pervasively affect the human brain at multiple levels, ranging from impaired molecular clearance to changes in structural and functional properties. Age-related changes in several sleep characteristics indicate that reduced sleep quality is a normal characteristic of aging. Conversely, sleep disruption may accelerate the aging process, yet it is not known whether sleep deprivation and sleep restriction may affect the apparent age status of the brain.

**Methods:** To tackle this question, we employed the concept of "brain age" to investigate whether the brain morphological response to sleep loss may cause the age-related changes of the brain, where the well-trained brain age model combines machine-learning algorithms and T1-weighted MRI features to predict the chronological age. First, we applied the publicly available brainageR model v2.1 to multiple datasets of different controlled total and partial sleep restriction conditions collected in 134 young healthy volunteers (mean chronological age of 25.3, between age of 19 and 39). Then, we analyzed the effects of sleep loss on brain age in these datasets.

**Results:** In three different datasets, we consistently observed that total sleep deprivation (TSD, > 24 h of prolonged wakefulness) increased brain age by 1–2 years regarding the group mean difference. After one night of recovery sleep following TSD, brain age decreased and was not different from baseline. We also demonstrated the associations between the change of brain age after TSD and several sleep variables. By contrast, brain age was not changed by neither acute (3 h' time-in-bed for 1 night) nor chronic partial sleep restriction (5 h' time-in-bed for 5 continuous nights).

**Conclusion:** Taken together, the convergent findings indicate that acute total sleep loss changes brain morphology in an aging-like direction in young samples and that these changes are reversible by recovery sleep.

**Disclosure**: No

### O237/P677 | Comparison of sleep deprivation and a low dose of ketamine on sleep and the EEG of rats under constant darkness

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**Introduction:** Sleep plays a critical role in mental health, and disturbed sleep is a well-known risk factor. This bi-directional link between sleep and emotions is complex and not well understood. Sleep deprivation (SD) in depressed patients can improve mood for a short period and works faster than traditional therapies that can take weeks to establish an antidepressant effect. Similar fast effects can be achieved with ketamine, a N-methyl-D-aspartate receptor antagonist. Since SD and ketamine both have an antidepressant effect, a comparison, from a sleep and chronobiological perspective, between these two treatments may provide more insights into the working mechanisms.

**Methods:** We performed electroencephalogram (EEG)/electromyogram recordings under constant darkness in Brown Norway rats and investigated the effect of SD which was performed between circadian time (CT) 0 – CT 6 and a low dose ketamine treatment (25 mg/kg) or saline control at CT 1.

**Results:** After SD, the animals showed increased sleep for at least 12 h ($n = 10$, $p < 0{,}0001$, two-way repeated measures ANOVA); after ketamine administration, the animals were awake and active for 2 h followed by increased Non-rapid eye movement (NREM) sleep ($n = 10$, $p < 0{,}0001$, two-way ANOVA), but not REM sleep. Both ketamine and SD induced an increase in EEG slow wave activity (1,0–4,0 Hz) during NREM sleep. We further analyzed the EEG power spectrum of NREM sleep and found that after SD the slow-wave peak frequency was faster compared to baseline ($n = 8$, $p < 0{,}0001$, after two-way ANOVA), but that this was not the case after ketamine administration. A similar result was obtained for the waking theta peak frequency, which was faster in the first 3 h after sleep deprivation, but not after ketamine treatment ($n = 8$, $p < 0{,}0001$, after two-way ANOVA). Effects on circadian phase of ketamine treatment at CT 1 are still under analysis.

**Conclusions:** The data show similar effects of both SD and ketamine on sleep and EEG power density, but also slight difference on EEG peak frequencies, suggesting that increased sleep pressure is the corresponding result between the two treatments.

**Disclosure**: No

## 12: INSTRUMENTATION AND METHODOLOGY (BASIC SLEEP SCIENCE)

### O019/P068 | How down-phase targeted auditory stimulation affects slow-wave activity, sigma activity and sleep-dependent memory consolidation

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**Background:** Slow waves (0.5–4 Hz), together with sleep spindles (11–16 Hz), have been implicated in the consolidation of declarative memory during sleep. We wondered how down-phase targeted auditory stimulation (DTPAS), despite initial evidence of reducing slow waves, affects slow-wave activity (SWA), sigma activity, and consequently sleep-dependent memory consolidation.

**Methods:** We recorded high-density electroencephalography (HD-EEG) in 21 young healthy adults in a night with and without DPTAS. In study 1 ($N = 14$), auditory stimuli were presented using on-ear headphones during ON windows (16 s), allowing stimulation, which took turns with OFF windows (8 s), withholding stimulation. In study2 ($N = 7$), more quiet auditory stimuli were presented using loudspeakers in longer ON (32 s) and OFF (16 s) windows. Sleep-dependent memory consolidation was tested using an associative word-pair memory task (40 word-pairs).

**Results:** Time-frequency analyses performed across the cortex showed that DPTAS increased SWA (1–4 Hz), theta (4–8 Hz), and beta (16–25 Hz) activity directly after stimulus presentation, as well as sigma activity (14–16 Hz) approximately one second later, strongest in a region around CZ (study 1). This sigma increase coincided with the positive peak of the induced auditory evoked potential. In line with this increase, more word-pairs were recalled after a night with DPTAS compared to SHAM, $t(12) = 2.59$, $p = 0.024$. When using more quiet stimuli (study 2), preliminary analysis indicated no changes directly after stimulus presentation. Instead, OFF windows showed a decrease of SWA compared to a SHAM night in a central cluster of 19 electrodes, $p < 0.05$. In line with this decrease, less word-pairs were recalled, $t(6) = -3.28$, $p = 0.017$.

**Conclusions:** We show, for the first time, that DPTAS can both in- and decrease SWA. These results suggest that features of auditory stimulation other than phase co-determine the effect of DPTAS on slow waves. We hypothesize that louder stimuli, independent of phase, evoke a K-complex-like response resulting in increased SWA, sigma activity and boosted memory consolidation. Quieter stimuli targeting the down-phase, on the other hand, may decrease SWA, the underlying mechanism of which remains to be uncovered.

The project is funded by the Swiss National Science Foundation and the HMZ Flagship Project "SleepLoop" of the University Medicine Zurich Switzerland.

**Disclosure**: No

## 13: COMPUTATION/MODELLING

### O147/P391 | Modelling age-related changes in human sleep across the 24 h-cycle: Impact of circadian amplitude and wake-promoting inputs to the monoaminergic system

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**Objectives/Introduction:** Ageing goes along with advanced sleep timing and reduced sleep consolidation. The objective of this study was to further probe the mechanisms of age-related changes in sleep-wake regulation, such as altered circadian sleep-wake-propensity and build-up of homeostatic sleep pressure.

**Methods:** To achieve this objective, we use an interdisciplinary approach combining experimental data and biophysical modelling. Ninety four healthy older adults (69 ± 5.4 years, 34% female) underwent a 40 h multiple nap protocol (10 short sleep-wake cycles of 160 min of wake and 80 min of nap opportunity), preceded and followed by an 8 h night-time sleep opportunity. In-lab polysomnography over sleep and nap opportunities was used to derive sleep efficiencies and onsets. Data were confronted to a model of arousal dynamics (Postnova et al., 2018), which was previously used to account for circadian and sleep-dependent homeostatic modulations in healthy young individuals. We assessed whether adapting physiologically-relevant model parameters could accommodate for observed changes in the aged. Three relevant model parameters were modified: circadian amplitude, rate of homeostatic sleep pressure build-up, and wake-promoting (cholinergic and orexinergic) input to monoaminergic nuclei. Agreement between model predictions and group averaged experimental measurements were quantified by root mean-squared error (RMSE).

**Results:** As expected, predictions made with the model tuned on data from young adults did not agree with the measurements for the older adults (RMSE = 1.31). Compared to the data, the model predicted higher sleep efficiencies during the biological night (baseline night and naps) and lower sleep efficiencies during the wake maintenance zone. Our data, from older adults, were best predicted by reducing simultaneously the parameters reflecting circadian amplitude and the wake-promoting input to the monoaminergic system (RMSE = 0.52). Tuning other parameters, such as the homeostatic time constant, did not improve agreement.

**Conclusions:** Our results suggest that ageing goes along with decreased amplitude of the circadian drive, together with an altered cholinergic/orexinergic input to the monoaminergic system. The latter might reflect decreased wake-state stabilization, a mechanism by which higher prevalence of daytime napping at older age can potentially be explained.

**Disclosure**: Yes

**Conflict of Interest statement:** The authors have no conflict of interest to disclose.

**Sources of funding:** Belgian Fund for Scientific Research (FNRS/BIG-SLEEP-T022020F), European Research Council (ERC-Starting Grant/COGNAP-GA 757763).

## 14: SLEEP DISORDERS - BREATHING

### O004/P095 | Nocturnal hypoxia and sleep fragmentation may drive neurodegenerative processes: compared effects of obstructive sleep apnea syndrome and periodic limb movement disorder on alzheimer's disease biomarkers

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**Introduction:** Sleep disorders may cause dysregulation of cerebral glucose metabolism and synaptic functions, as well as alterations in cerebrospinal fluid (CSF) biomarker levels. This study aimed at measuring sleep, CSF Alzheimer's disease (AD) biomarkers, and cerebral glucose consumption in patients with obstructive sleep apnoea syndrome (OSAS) and patients with periodic limb movement disorder (PLMD), compared to controls.

**Methods:** OSAS and PLMD patients underwent 18F-fluoro-2-deoxy-D-glucose positron emission tomography ($^{18}$F-FDG PET), polysomnographic monitoring and lumbar puncture to quantify CSF levels of $\beta$-amyloid$_{42}$ (A$\beta_{42}$), total tau, and phosphorylated tau. All patients were compared to controls, who were not affected by sleep or neurodegenerative disorders.

**Results:** Twenty OSAS patients, 12 PLMD patients and 15 controls were included. Sleep quality and sleep structure were altered in both OSAS and PLMD patients when compared to controls. OSAS and PLMD patients showed lower CSF A$\beta_{42}$ levels than controls. OSAS patients showed a significant increase in glucose uptake in a wide cluster of temporal-frontal areas and cerebellum, as well as a reduced glucose consumption in temporal-parietal regions compared to controls. PLMD patients showed increased brain glucose consumption in the left Para hippocampal gyrus and left caudate than controls.

**Conclusions:** Sleep dysregulation and nocturnal hypoxia present in OSAS patients, more than sleep fragmentation in PLMD patients, were associated with the alteration in CSF and $^{18}$F-FDG PET AD biomarkers, namely reduction of CSF A$\beta_{42}$ levels and cerebral glucose metabolism dysregulation mainly in temporal areas, thus highlighting the possible role of sleep disorders in driving neurodegenerative processes typical of AD pathology.

**Financial support:** None

**Conflict of interest:** The authors report no conflicts of interest or financial disclosures.

**Disclosure**: No

## O006/P096 | Cluster analysis of specific sleep apnoea phenotypes in women: results from the esada cohort

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**Objectives/Introduction:** Cluster analysis in Obstructive Sleep Apnoea (OSA) patients are conducted in order to reveal the diversity and heterogeneity of the disease and allow personalized management. The current study aimed to identify specific OSA phenotypes in women in the ESADA pan European database.

**Methods:** Latent class analysis was applied to data from 9,710 females among the 32,700 ESADA participants. Clusters were built and identified by including the following variables: age, Body Mass Index (BMI), Apnea Hypopnea Index (AHI), Epworth Sleepiness Scale (ESS), co-morbidities (cardiovascular, pulmonary, psychiatric, metabolic, other). Comparisons between clusters were performed by using non-parametric Kruskal–Wallis tests for quantitative variables and chi-square or Fisher's exact test for qualitative variables.

**Results:** Four clusters were identified:

Cluster 1 "Females with ischemic heart disease" (38.3%): the largest cluster characterized by ischemic heart disease (56%), middle aged women, overweight, with moderate OSA, median AHI: [IQR] 22.9/h [17.4; 30], non-sleepy(Epworth Sleepiness Scale (ESS): 9 [5; 12]).

Cluster 2 "Elderly, females with co-morbidities" (23%): elevated AHI 46/h [30; 60.1], nocturnal hypoxia with time spent at $SaO_2$ < 90%: 40.6 min [10.1; 104.7], non-sleepy (ESS: 9 [6; 13]) and with high degree of co-morbidities (hypertension, diabetes, hyperlipidemia, COPD, neurologic, others).

Cluster 3: "Sleepy obese females" (16.2 %): middle aged, presenting the highest BMI: 43 [37.6; 48.9] kg/m$^2$ and AHI: 53.3/h [32; 80.5], most sleepy (ESS: 12 [8; 16]), with essentially associated psychiatric disease (22.7%) and asthma (13.9%).

Cluster 4: "Females with insomnia and mild OSA" (22.5 %): middle aged, overweight with low AHI, with insomnia and non-sleepy (ESS: 9 [5; 13]), presenting low frequency of co-morbidities. Positive airway pressure (PAP) was prescribed to the majority of patients in Cluster 1 (77.3%), Cluster 2 (92.1%) and Cluster 3 (91.7%). In Cluster 4, 23.8% were treated with PAP and 15% with mandibular advancement devices (MAD). CPAP adherence > 4 h was highest in Cluster 1 (85.5%) and Cluster 2 (87%).

**Conclusion:** Four distinct clinical OSA phenotypes were identified in the female patients of a large pan-European database highlighting the importance of gender-based phenotypes and their impact on patient's risk stratification and individualized treatment.

**Disclosure**: No

O007/P097 | **"Blow or bite" - treatment recommendations in mild to moderate obstructive sleep apnea in the european sleep apnea database cohort**

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**Introduction:** Mild and moderate obstructive sleep apnea (OSA), defined as apnea/hypopnea-event frequency (AHI) between 5 < 15 and 15 < 30 events/h of sleep, respectively, are frequently diagnosed. Treatment with both positive airway pressure (PAP) or oral devices (OD) is recommended in several guidelines. While PAP is more effective in respiratory event control, improvement in symptomatology is comparable between the two modalities. Data suggest better adherence with OD when compared with PAP-treatment. Our study aimed to analyse predictors for treatment recommendations in mild-to-moderate OSA from the multicentric European Sleep Apnea Database (ESADA) cohort.

**Methods:** The phenotypic factors associated with OD- instead of PAP treatment were analysed in the ESADA cohort. Consecutive patients with mild and moderate OSA ($N = 1699$ and 4308, respectively) and with a treatment recommendation for PAP or OD were included. A multivariable logistic regression model was performed, including predictors like anthropometrics (age, gender, Body Mass Index [BMI]), symptoms (Epworth Sleepiness Scale score [ESS]), apnea severity (AHI, lowest saturation), and comorbid hypertension.

**Results:** 25 out of 30 ESADA centers (83%) prescribed OD as first line treatment. Prescription rate for OD was approximately 10% in 5 and exceeded 15%–20% in 3 centers. Female gender was a significant predictor for OD treatment (Odds ratio mild OSA 1.35 (95% CI 1.08–1.70, $p = 0.01$) and moderate OSA 1.38 (95% CI 1.07–1.78, $p = 0.013$), respectively). Age (Beta −0.039 and −0.039), BMI (Beta −0.06 and −0.11), AHI (Beta −0.10 and −0,20) and ESS (Beta −0.0 and −0.08) were all significant predictors for OD treatment, respectively ($p < 0.001$ for all factors). Limited apnea related hypoxia (lowest saturation with Beta 0.049, $p < 0.001$) was a predictor for OD only in mild OSA. Comorbid hypertension was not associated with treatment recommendations.

**Conclusion:** Treatment in mild-to-moderate OSA favors PAP over OD. Anthropometric factors, symptoms and OSA severity influenced the treatment choice. Geographical differences, availability and reimbursement models for each treatment option may also influence both patients' and doctors' decisions and need to be further evaluated. Data on clinical outcomes are warranted to recommend one treatment modality over the other.

**Disclosure**: Yes

**Conflict of Interest statement:** Related to the submitted work: Scientific collaboration of the ESADA group with Bayer AG; Outside the submitted work: Speakers bureau for Resmed, Philips, Somnomed, Astra Zeneca, Lundbeck. Share owner of a company with a patent licensed for treatment of sleep apnea (Desitin GMBH).

O008/P098 | **Obstructive sleep apnoea symptom subtypes and hypoxic burden independently predict distinct cardiovascular outcomes**

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**Objectives/Introduction:** Studies on heterogeneity of obstructive sleep apnea (OSA) have identified and validated clinically relevant symptom-based subtypes (minimally symptomatic, disturbed sleep, moderately sleepy and excessively sleepy) and novel OSA-specific nocturnal hypoxemia measures. Evidence suggests that excessively sleepy moderate-severe OSA patients have increased risk of incident major adverse cardiovascular events (MACE; composite of coronary heart disease, heart failure, stroke or cardiovascular mortality) and that OSA-specific hypoxic burden (HB) is associated with increased risk of cardiovascular disease (CVD) mortality. This study provides a systematic assessment of individual and combined contributions of these factors on incident risk of different CVD outcomes, addressing an important gap in current evidence.

**Methods:** Participants from the Sleep Heart Health Study with high-quality oxygen saturation, OSA severity quantified by apnea-hypopnea index (AHI), and symptom data were included. Latent class analysis on 14 symptoms was used to classify participants with moderate-severe OSA (AHI ≥ 15) into subtypes. HB was calculated from respiratory event related hypoxia and total sleep time. Cox proportional hazards models were used to assess associations between OSA severity, symptom subtypes and log-transformed HB with CVD mortality and MACE, adjusted for demographic and CVD risk factors. Analyses were performed in CVD-free participants and all participants adjusted for baseline CVD presence. Of particular interest was whether symptom subtypes and/or HB were associated with CVD outcomes independent of each other.

**Results:** 5,027 participants were analyzed with median follow-up of 11.6 years (CVD mortality) and 11.3 years (MACE). HB was independently associated with CVD mortality in all participants (HR = 1.44; 95%CI = 1.06–1.97; $p$ = 0.021) and CVD-free participants (HR = 1.62; 95%CI = 1.12–2.35, $p$ = 0.010) controlling for symptom subtype. On the other hand, symptom subtypes were independently associated with MACE incidence only among CVD-free participants, controlling for HB, with the excessively sleepy participants having significantly higher risk of MACE (HR = 1.98; 95%CI = 1.26–3.10, $p$ = 0.003) compared to those without OSA.

**Conclusions:** OSA symptom subtypes and HB are independently associated with specific CVD-related endpoints. Higher HB was associated with cardiovascular mortality, controlling for symptom subtype. The excessively sleepy subtype was at higher risk of new MACE, controlling for HB. Thus, both of these factors are important for understanding OSA-related CVD risk.

**Disclosure**: No

## O009/P099 | Sulthiame improves sleep quality in patients with moderate-to-severe obstructive sleep apnea– a randomized placebo-controlled trial

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**Introduction:** Sulthiame (STM), a potent carbonic anhydrase inhibitor, reduced the apnea-hypopnea index (AHI) in patients with obstructive sleep apnea (OSA).[1] We studied the effect of STM on sleep quality assessed by cardiopulmonary coupling (CPC) in OSA patients not tolerating positive airway pressure treatment.

**Methods:** Post-hoc analysis of a double-blind, placebo-controlled, phase IIb trial ($n$ = 58, 72% male, age 60 ± 10 years, body mass index 28 ± 3 kg/m$^2$, AHI 56 ± 22 events/h).[1] Patients were randomized to receive placebo ($n$ = 22), STM 200 mg ($n$ = 11), or STM 400 mg ($n$ = 25). Polysomnography recordings were performed at baseline and after 4 weeks of intervention. The electrocardiography signal from sleep studies was used for CPC analysis. The proportion of high-frequency coupling (HFC, stable sleep), low-frequency coupling (LFC, unstable sleep), elevated-LFC narrow-band (e-LFC$_{NB}$, marker of periodic breathing) and elevated-LFC broad-band (e-LFC$_{BB}$, sleep fragmentation) was calculated. Patient-reported outcome measures (PROMs) was assessed by Functional Outcomes of Sleep Questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS). The changes in CPC variables between STM 200/400 mg and placebo were analyzed using analysis of covariance.

**Results:** Baseline arousal index did not differ between groups and was significantly reduced after STM treatment. Compared to placebo, STM 200 mg significantly reduced LFC (0.9 ± 11.4 vs.12.2 ± 16.0%, $p$ = 0.026) and e-LFC$_{BB}$ (0.4 ± 8.5 vs. 9.1 ± 4.5%, $p$ = 0.003). The corresponding changes for STM 400 mg were 6.7 ± 11.3% and 4.8 ± 10.5%, ($p$ = 0.089 and 0.13, respectively). HFC and e-LFC$_{NB}$ did not change by the STM treatment. Arousal index reduction was significantly correlated with the drop of e-LFC$_{BB}$ ($r$ = 0.39, $p$ = 0.020). Changes of HFC, LFC and e-LFC$_{BB}$ were associated with improvement of FOSQ total score after STM treatment ($n$ = 36, $r$ = 0.36, −0.35 and −0.34, $p$ = 0.032, 0.038 and 0.041, respectively). Decrease of e-LFC$_{BB}$ was correlated with ESS reduction in the STM 200 mg group ($r$ = 0.64. $p$ = 0.034).

**Conclusions:** STM reduces sleep fragmentation and improves sleep quality assessed by CPC. Nocturnal CPC analysis provide novel insights on treatment effect of PROMs in OSA patients. (EudraCT: 2017-004767-13)

[1]Hedner et al. A randomized controlled trial exploring safety and tolerability of sulthiame in sleep apnea. AJRCCM 2022. In press.

**Disclosure**: Yes

**Conflict of Interest statement:** KT, CS and DZ report no conflict of interest. JH, KS and LG are shareholders in Cereus Pharma AB, which owns the license for sulthiame in OSA.

## O010/P100 | Association of conventional polysomnographic metrics of obstructive sleep apnea with major adverse cardiovascular events: a prospective sleep clinic cohort study

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**Background:** Obstructive sleep apnea (OSA) is associated with major adverse cardiovascular events (MACE), but it is unclear which conventional polysomnography (PSG) metrics of OSA severity best predict future MACE, and whether associations vary by age, sex, and prevalent cardiovascular disease (CVD).

**Methods:** A cohort of 4,067 adults who completed diagnostic PSG between 2006 and 2010 at a tertiary sleep clinic (Perth, Australia) were prospectively followed-up for MACE (composite outcome: cardiovascular death or first non-fatal hospitalization during follow-up for coronary, cerebrovascular or peripheral vascular disease, heart failure, or atrial fibrillation), identified from individual-linked hospitalization and mortality data to 1 January 2016.

The associations between PSG metrics of OSA and MACE in the whole cohort and in sub-groups stratified by age-group (< 60 years, ≥60 years), sex, and prevalent CVD were investigated using multivariable-adjusted Cox regression models. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CI).

PSG metrics assessed included apnea-hypopnea index (AHI), time in min spent with oxygen saturation < 90% (T90), oxygen desaturation index 3% and 4% (ODI3, ODI4), and arousal index. Metrics with skewed distribution were $\log_e$-transformed prior to analysis.

**Results:** The study cohort was middle-aged (50.6 ± 14.0 years), obese (32.7 ± 7.7 kg/m$^2$), and 60.8% male. Across the cohort, 85.6% ($n = 3{,}815$) were diagnosed with OSA (AHI≥5 events/hr), and 45.1% ($n = 1{,}835$) had severe OSA (AHI ≥ 30 events/hr).

Over a median follow-up of 7.2 years, 14.3% ($n = 582$) developed MACE. After multivariable adjustment for known CVD risk factors, log-transformed PSG metrics of hypoxemia, but not AHI, predicted the development of MACE: T90 (HR, 1.14; 95%CI, 1.00–1.29), ODI3 (HR, 1.34; 95%CI, 1.03–1.75), and ODI4 (HR, 1.27; 95%CI, 1.02–1.59) (all $p < 0.05$). PSG metrics of OSA severity were independently associated with MACE primarily in individuals aged < 60 years, women, and those with prevalent CVD.

**Conclusions:** In this large prospective sleep clinic cohort, PSG metrics of hypoxemia, but not AHI, were independently predictive of MACE. Analyses by clinical sub-groups suggest that physiological insults related to OSA, as measured by PSG metrics, are more likely to be significantly associated with MACE in middle-aged or younger adults, women, and in those with prior CVD.

**Disclosure**: Yes

**Conflict of Interest statement:** Jennifer Walsh and Kathleen Maddison have received research funding from Nyxoah SA and Incannex Healthcare Ltd but have nothing to disclose which is relevant to the content of this abstract. Brendan McQuillan has received honoraria for advisory board participation and education meetings from AstraZeneca and Boehringer Ingelheim Lily. Nigel McArdle has received research funding support within the last year from Nyxoah Pty Ltd (Mont-Saint Guibert, Belgium). All other authors have no conflicts of interest to declare.

## O011/P101 | Characterization of paediatric heart rate variability segments based on sleep stage and presence of apnoeic events

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**Introduction:** Heart Rate Variability (HRV) activity in children changes across sleep stages and in the presence of apnoeic events. While previous studies compared HRV during sleep stages between OSA and healthy children, a segment-level characterization, regardless children diagnosis, has not been performed. In this context, a paediatric OSA-specific spectral band (BW2, 0.028–0.074 Hz), within very low frequency (VLF, 0–0.04 Hz) and low frequency (LF, 0.04–0.15 Hz), has been recently identified. However, BW2 evolution across sleep stages has not been evaluated. Our aim is to characterize and compare HRV segments in VLF, LF and BW2 bands based on sleep stages (NREM; REM and Wake) and the changes related to increased respiratory events presence.

**Methods:** A total of 1018 children (5–9.9 years) from the Childhood Adenotonsillectomy Trial were included. Overnight electrocardiogram recordings were segmented into 10-min epochs and categorized as Wake, NREM, or REM. Segments were also marked as control (no apnoeic events), mild OSA (1 to 5 events), moderate OSA (5 to 10 events) or severe OSA (over 10 events). VLF, LF, and BW2 activity for each segment were measured, and intra and inter-group comparisons were performed.

**Results:** BW2 and LF bands showed statistically significant differences in NREM sleep between all groups when separated by apnoeic events number ($p$-value < $10^{-20}$), with the highest difference found in BW2 between control and severe OSA segments (median values 0.12 vs 0.39, respectively). For REM sleep, BW2 also showed improved and statistically significant differences between groups when separated by apnoeic event counts than LF and VLF. However, these differences were less prominent than in NREM, even though there is clustering of respiratory events during REM sleep.

Regarding sleep stages, only BW2 band showed no differences between REM and Wake in control segments. All the other comparisons showed statistically significant differences.

**Conclusions:** REM sleep is associated with enhanced sympathetic activity which may be masking the effect of apnoeic events on HRV. Therefore, alterations due to apnoeic events are better captured through the novel BW2 band during NREM, while in the absence of apnoeic events, sleep stages are better differentiated through VLF and LF classic bands.

**Disclosure**: Yes

**Conflict of Interest statement:** The authors declare no conflict of interests.

This abstract was supported by CIBER-BBN (ISCIII), cofounded with "European Regional Development Fund" (FEDER), as well as under the project Sleepy Heart from 2020 CIBER-BBN valorization call, by the "Ministerio de Ciencia, Innovación y Universidades" and FEDER under projects PID2020-115468RB-I00, and PDC2021-120775, and by Gobierno de Aragón (Reference Group BSICoS T39-20R). Adrián Martín-Montero was in receipt of a "Ayudas para contratos predoctorales para la Formación de Doctores" grant from the Ministerio de Ciencia, Innovación y Universidades (PRE2018-085219). David Gozal and Leila Kheirandish-Gozal are supported by the Leda J Sears Foundation, and a Tier 2 grant from the University of Missouri.

## O037/P102 | PAP treatment adherence supported by dietary intervention is improved in overweight and obese obstructive sleep apnea (OSA) Patients: a randomized, controlled trial

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**Objectives:** To explore the role of diet intervention on Positive airway pressure (PAP) treatment adherence in patients with obstructive sleep apnea (OSA). Specifically, we evaluated the effects of a combination of PAP and weight-loss Mediterranean diet intervention on improving PAP adherence, Body mass index ($BMI$), daytime symptoms, mainly sleepiness and arterial blood pressure measurements over the effect of standard care alone.

**Methods:** We designed a parallel, randomized, controlled, clinical trial. Eligible participants were adult, overweight and obese men and women, diagnosed with moderate-to-severe OSA [apnea-hypopnea index (AHI) ≥ 15 events/h] through an attended overnight polysomnography. Participants, after written informed consent, were blindly randomized to a standard care group (SCG, $n = 25$) and a Mediterranean diet group (MDG, $n = 24$). Study groups were prescribed PAP. The SCG received oral healthy lifestyle advice and counseling on physical activity and sleep habits, while the MDG was additionally subjected to a 6-month behavioral intervention aiming at weight loss and increasing adherence to the Mediterranean diet. PAP adherence (hours of device use), BMI, daytime sleepiness, evaluated by Epworth Sleepiness Scale (ESS) and arterial blood pressure measurements were evaluated pre- and post-intervention.

**Results:** No statistically significant changes were noted between the 2 groups in clinical characteristics or sleep study parameters. Post intervention PAP use was higher in the MDG group compared to SCG (6.5 ± 3 vs 5.7 ± 2, $p = 0.2$), although the difference wasn't statistically significant. However, further analysis showed that diet intervention was the most significant predictive factor for improved PAP adherence (OR = 19.910, 95% CI = 1.349–293.919, $p = 0.02$). Regarding BMI, an increase was noted in the SCG group, whereas a decrease (improvement) in the MDG, although not statistically significant ($p = 0.31$). Blood pressure measurements were not significantly changed after the 6 month follow period in both groups. Despite the significant decrease in ESS noted in both groups, no group had a significant predominance in this improvement ($p = 0.29$).

**Conclusions:** A dietary intervention on top of standard care leads to greater improvements in PAP adherence compared to standard care alone, suggesting intensive support with increased time spent in the MDG group could be worthwhile for improving PAP compliance.

**Disclosure**: No

## O039/P103 | Comparison between non-sleepy patients diagnosed with obstructive sleep apnea by polysomnography versus non-sleepy patients who underwent home sleep apnea test

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**Objectives/Introduction:** According to American Academy of Sleep Medicine Clinical Practice Guideline (2017) Home Sleep Apnea Test (HSAT) is recommended in case of increased risk of moderate to severe Obstructive Sleep Apnea(OSA), indicated by the presence of excessive daytime sleepiness (EDS) and at least two of the following three criteria: loud snoring; witnessed apnea or gasping; or diagnosed hypertension. EDS is absent in many individuals with significant sleep-disordered breathing. The aim of this study was to evaluate OSA patients diagnosed by HSAT, despite the absence of EDS and to compare with patients diagnosed by polysomnography (PSG). Statistical analysis performed by SPSS v 20.0, $p$ value 0.05.

**Methods:** A total of 187 patients who did not suffer from EDS and diagnosed with 0SA (Apnea-Hypopnea Index (AHI) ≥ 5 events/h) participated in this study. 156 patients underwent an attended PSG whereas 31 underwent a type III HSAT. Sleepiness was assessed with the Epworth Sleepiness Scale (ESS). Patients without EDS were defined as they had an ESS score < 10.

**Results:** The non-sleepy patients who diagnosed after an attended PSG did not differ on mean age (55.42 ± 13.34 years vs 54.10 ± 14.50, $p = 0.62$), on ESS score [ESS median (interquartile range) = 6(4–7) vs 5(4–8), $p = 0.93$)] or on BMI [BMI median(interquartile range) = 29.2(27–33.48) vs 29.2(27–34.3) kg/m$^2$, $p = 0.79$] compared to non-sleepy OSA patients who diagnosed by HSAT. Interestingly, two groups did not differ on AHI [AHI median (interquartile range) = 28(11–48.75) vs 21 (6–59) events/h, $p = 0.41$], on minimum $O_2$saturation level [saturation median (interquartile range) = 84 (80–88) vs 85(73–90)%, $p = 0.88$] or on their comorbidities. Non-sleepy HSAT group presented with increased percentage of nocturnal jerks (12% vs. 1.28%, $p = 0.007$) compared to PSG group. On the contrary, patients diagnosed by PSG report higher percentage of the daytime symptoms: attention difficulties (50.6% vs. 12.9%, $p = 0.00$) and concentration difficulties (50.6% vs. 19.35%, $p = 0.001$) compared to HSAT group.

**Conclusions:** OSA patients without EDS diagnosed by HSAT did not differ on AHI or on minimum $O_2$Saturation level compared to non-sleepy patients diagnosed by PSG. Non-sleepy OSA patients diagnosed by PSG presented with increased percentage of attention and concentration difficulties compared to HSAT group.

**Disclosure**: No

## O040/P104 | Continuous positive airway pressure treatment in obese patients with sleep apnea syndrome: the effect on basal metabolic rate

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**Objectives:** To assess the effect of the continuous positive airway pressure (CPAP) treatment on basal metabolic rate (BMR) in obese patients with obstructive sleep apnea syndrome (OSAS).

**Method:** In included patients, demographic characteristics, body mass index (BMI), apnea-hypopnea index (AHI) and parameters of nocturnal hypoxemia (all assessed via polysomnography), Epworth sleepiness scale (ESS), arterial blood gases, lipidemic profile, LDH, SGOT, SGPT, uric acid and CRP were recorded. Basal metabolic rate, oxygen consumption and carbon dioxide output levels were assessed via indirect calorimetry and compared before and after C-PAP administration (after the first night of titration, after one and three months of treatment).

**Results:** 21 obese patients (18 men, 3 women, mean BMI: 39,7 kg/$m^2$) were included, with a median age of 54(41–70) years and mean AHI: 69/h. Positive correlations were found between $BMR_0$ and ESS ($p = 0.252$), $PCO_2$ ($p = 0.239$), Time < 90%($p = 0.251$), BMI ($p = 0.127$) and negative correlations between $BMR_0$ and $PO_2$ ($p = -0.286$), $HCO_3$ ($p = -0.092$), FVC ($p = -0.031$), MeanSat ($p = -0.063$) and minSat($p = -0.25$) during sleep.

A repeated ANOVA was used to investigate whether there was a decrease in BMR after the intervention. No statistically significant differences were found across four time points [$F(1, 18) = 1.429$, $p = 0.269$]. A decrease was observed, but due to the small sample size this difference was not found to be statistically significant.

**Conclusion:** This study suggests there is a reduction in BMR after C-PAP treatment. More data on the relationship between OSA, obesity and BMR, as well as the effect of C-PAP treatment on energy expenditure are required.

**Disclosure**: No

## O076/P413 | "Beyond the AHI" – new swedish guidelines using a matrix for treatment indication in obstructive sleep apnea

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**Introduction:** The Apnea Hypopnea Index (AHI) is frequently used as single parameter for obstructive sleep apnea (OSA) severity classification (mild, moderate and severe for AHI thresholds 5- < 15, 15- < 30, and ≥30 events/h). This classification is poorly associated with patients' symptomatology and long-term outcome (Pevernagie, JSR 2021). Recently, four classes of sleep apnea severity have been proposed based on OSA symptoms (yes/no) and comorbidities (absence or well controlled/uncontrolled), the so called "Baveno classification" (Randerath, ERJ 2018). Distribution of patients by four classes A-D in this novel matrix has been explored in the European Sleep Apnea Database Cohort (Randerath, PLOS One 2020). Interestingly, over 80% of OSA patients were treated with CPAP irrespective of the A-D severity classification.

In the new Swedish Guidelines for OSA treatment we aimed to develop a matrix based on evidence from treatment outcome studies.

**Methods:** The task force, initiated by the National Sleep Apnea Registry (SESAR), included specialists in pulmonary, ear nose throat, neurology/neurophysiology, cardiology and dental medicine and members with several professional backgrounds (physicians, dentists, nurses, patient group representatives). A Delphi-round was performed by distributing the draft version amongst experts in all Swedish regions. The work was supported by grants from the Swedish Association of Local Authorities and Regions.

**Results:** The novel matrix includes 24 classes varying between very weak, weak, moderate, strong and very strong treatment indication. The matrix includes several layers of decision points including

(A) OSA related symptoms,
(B) cardio metabolic comorbidities,
(C) frequency of respiratory events and
(D) age.

OSA related symptoms always implicate indication for treatment (moderate to very strong) whereas absence of symptoms, age above 65 years, and no/well controlled comorbidity constitute weak/very weak treatment indication irrespective of AHI.

**Conclusion:** The novel treatment matrix is based on current evidence on expected treatment outcomes rather than the frequency of respiratory events during sleep alone. The new matrix was published in December 2021 and strategies for nationwide implementation are ongoing. Prospective evaluation of treatment outcomes is warranted and the structure with a national quality registry (SESAR) constitutes the basis for this task.

**Disclosure**: Yes

**Conflict of Interest statement:** LG: Outside the submitted work: Speakers bureau for Resmed, Philips, Somnomed, Astra Zeneca,

Lundbeck. Share owner of a company with a patent licensed for treatment of sleep apnea (Desitin GMBH).

## O077/P414 | Reduced loop gain after sulthiame in patients with moderate to severe OSA

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**Background:** Mechanical methods constitute the primary therapy in obstructive sleep apnea (OSA). An effective and well-tolerated pharmacological alternative is much needed. Sulthiame (STM), a carbonic anhydrase (CA) inhibitor has been applied in OSA (Hedner et al. AJRCCM 2022). Recent research has used sleep recordings to identify specific endotypic traits which may explain a diversity of OSA pathologies. Deeper understanding of these mechanisms may enable precision medicine in OSA management.

**Methods:** Post-hoc analysis of a double-blind, randomized, placebo-controlled dose guiding, safety and tolerability study of STM in 68 patients with moderate/severe OSA. Patients were 18–75 years old, with BMI 20–35 kg/m$^2$, apnea hypopnea index (AHI) ≥15 events/h and had terminated OSA treatment due to non-tolerability. Exclusion criteria included conditions with central sleep apnea or uncontrolled hypertension. Polysomnography was performed during two consecutive nights before and after intervention. A target STM dose of 200 and 400 mg o.d. ($n$ = 12 and 24) or placebo ($n$ = 22) was established during 4 weeks by titration, yielding a stable dose during the last two weeks of follow-up. Loop gain (LG) during NREM sleep was determined from polysomnography using an established modelling of ventilatory drive during naturally occurring breathing disruptions (Terrill, ERJ, 2015). The difference from baseline to week 4 was analysed with baseline adjusted analysis of covariance.

**Results:** AHI (mean [SD]) at baseline was 53.9 (21.1), 61.1 (24.2) and 55.2 (22.3) events/h in the placebo, STM 200 mg and 400 mg groups, respectively. The change of the AHI during therapy in the three groups were −3.0 (10.5), −20.5 (14.2) and −22.2 (12.5) events/h, respectively, $p$ < 0,001 in both doses compared to placebo. Corresponding LG values at baseline were 0.56 (0.11), 0.58 (0.11) and 0.53 (0.10) and after intervention 0.56 (0.11), 0.45 (0.10) and 0.37 (0.06), respectively (STM 200 mg and 400 mg vs. placebo, all $p$ < 0.001).

**Conclusion:** In this randomized controlled study, a dose-dependent reduction of AHI and LG was demonstrated after STM treatment. The effect applies in most OSA patients studied and may be particularly pronounced in those with high LG. Further mechanistic studies on the effects of STM in OSA are warranted. (EudraCT N°: 2017-004767-13).

**Disclosure**: Yes

**Conflict of Interest statement:** EH, CS and DZ reports no conflict of interest to the current work. JH, LG and KS are shareholders of intellectual property regarding the substance tested in the study.

**Sources of support:** Desitin GmbH, Hamburg, Germany financed the clinical trial. Swedish Government Research Grant Research and Educational Grant LUA/ALF and Swedish Heart and Lung Foundation, research grants.

## O078/P415 | Ischemic preconditioning, a potential cardio protective mechanism of OSA during acute coronary syndrome

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**Background:** Sleep apnea (SA) is associated with intermittent hypoxemia that may lead to ischemic preconditioning in the myocardium. This potential cardio protective effect of SA may play a role in the development of non-ST-elevation myocardial infarction (NSTEMI) versus ST-elevation myocardial infarction (STEMI) during acute ischemia.

**Purpose:** We prospectively investigated the prevalence of these two types of MI in patients with SA.

**Methods:** We prospectively studied 607 consecutive patients admitted with the diagnosis of acute MI (both NSTEMI and STEMI). All subjects underwent sleep evaluations using a portable diagnostic device after at least 48 h post-admission, provided they were in stable condition.

**Results:** SA was present in 65.7% and NSTEMI in 30% of patients. The prevalence of NSTEMI increased with increasing severity of SA ($p$ < 0.001). The relative frequency of NSTEMI vs STEMI in patients without SA and with mild SA was 59.4% vs 70.1% respectively ($p$ = 0.01). In patients with moderate to severe SA (AHI ≥ 15events/h), the relative frequency of NSTEMI and STEMI was 40.6% vs 29.9% respectively ($p$ = 0.01). Moderate to severe SA was an independent predictor of having a NSTEMI ($p$ = 0.021). In moderate to severe SA patients, those with NSTEMI had lower peak troponin T than those with STEMI (1.538 ± 2.771 μg/l vs 3.085 ± 3.127 μg/l, $p$ < 0.001).

**Conclusion:** The prevalence of NSTEMI increases with increasing severity of SA. This finding may suggest a cardio protective role of SA, which may attenuate the development of STEMI, perhaps through ischemic preconditioning. Ischemic preconditioning is considered to be one of the causes of decreased cardiovascular mortality, especially in elderly patients with OSA, and may be involved in the ineffectiveness of CPAP in secondary prevention. Thus, ischemic preconditioning

can play an important role in a personalized approach to CPAP treatment in secondary prevention.

**Disclosure**: No

## O079/P416 | Long-term variability and reliability of physiological endotypic traits derived in clinical routine in patients with obstructive sleep apnea

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**Background:** The introduction of physiological endotypic traits (e.g., loop gain) might promote the development of precision medicine in obstructive sleep apnea (OSA). However, the role of night-to-night variability and the influence of sleep and position on endotypic traits have not been extensively studied. We applied an established endotyping methodology [1,2] in routine clinical polysomnography (PSG) studies and determined endotypic traits after 4 weeks of follow-up in patients with moderate-to-severe OSA.

**Methods:** Endotypic traits were evaluated in placebo treated subjects participating in a randomized controlled trial [3] ($n$ = 22; male 77%; age 61 ± 10 years; apnea-hypopnea index (AHI) 54 [35–69] events/h) from 2 × 2 in-lab PSGs (Embla A10 system; Flaga, Reykjavik, Iceland) at baseline and at a 4-week follow-up. Recordings were scored according to AASM criteria. Nasal flow, apnea/hypopnea events, and arousals during NREM sleep were classified and nine previously reported endotypic traits were determined, reflecting the ventilatory control system (VCS) (loop gain (LG1 and LGn), arousal threshold (ArTh), ventilator response to arousals (VRA), and time delay), and upper airway anatomy (UA) (Vactive, Vpassive, Vmin, and muscle compensation). Statistical analysis was performed using Wilcoxon signed rank test and intra-class correlation (ICC). Results for variability in endotypic traits are compared with the variability in AHI and ODI.

**Results:** The endotypic traits showed moderate to good reliability over the 4 weeks period (ICC: LGn = 0.63; VRA = 0.69; LG1 = 0.72; Vactive = 0.74*; delay = 0.87; Vmin = 0.88; Vpassive = 0.92*; ArThres = 0.93; [* skewed bias detected]), as did the AHI and ODI (ICC 0.89 and 0.88, respectively). Only the parameter "muscular compensation" showed poor reliability (ICC = 0.23) at 4 weeks follow up. None of the tested parameters showed a significant difference between assessments. In a sensitivity analysis performed during supine NREM-sleep ($n$ = 9 patients), UA-characteristics increased in reliability, while VCS-characteristics remained unchanged.

**Conclusion:** A series of novel endotypic traits showed strong agreement on repeated measures within 4 weeks, similarly to AHI and ODI. With the exception of muscle compensation, all tested parameters showed moderate to good reliability. Spontaneous variation in sleep position was identified as potential cause for increased variability.

**Disclosure**: No

## O080/P417 | eSATIS study: can treatment of sleep-disordered breathing improve cognitive recovery after stroke?

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**Objectives:** Sleep-disordered-breathing (SDB) and cognitive dysfunction are common after stroke. Considering the link between SDB and cognitive dysfunction, we aimed to investigate the impact of SDB treatment with adaptive servo-ventilation (ASV) on cognitive recovery from acute to subacute stroke.

**Methods:** This project is a part of eSATIS study (Duss et al, Trials 2021). eSATIS study included the patients without SDB (apnea-hypopnea index < 5/h) and with SDB (apnea-hypopnea index > = 20/h), who were randomized in treatment (SDB ASV+) and control (SDB ASV-) groups.

Demographics, stroke characteristics and sleep breathing (by respirography) were assessed at admission. Longitudinal assessments of cognitive functions were performed within 5 days post-stroke and at 3 months post-stroke and included tests for language, attention, executive functions, visual and verbal memory.

**Results:** 134 patients with complete cognitive assessment (age: 67.20 [58.05; 74.95] years; female sex: 48 (36%) patients; National Institute of Health Stroke Scale (NIHSS) score at admission: 5.00 [3.00; 10.00] points) were included in the current analysis.

SDB ($n$ = 73/134) versus no-SDB ($n$ = 61/134) was associated with cognitive deficits at acute stroke, affecting executive functions (Go/no Go: +2.00 errors, $p$ = 0.037) and short- and long-term visual memory (Brief Visuospatial memory test (BWMT) immediate recall: −3.57 points, $p$ = 0.043; BWMT delayed recall: −1.60 points, $p$ = 0.038), according to multiple linear regression adjusted for age, sex and relevant clinical characteristics (hypertension and obesity).

SDB ASV- ($n$ = 29/80) versus no-SDB ($n$ = 51/80) was not associated with the difference in cognitive functioning from acute to subacute stroke according to multiple linear regression adjusted for baseline cognitive parameters, age, sex and hypertension. However, SDB ASV+ ($n$ = 14/43) versus SDB ASV- ($n$ = 29/43) was associated with larger improvement in short-term visual memory (BWMT, immediate recall: +3.32 points, $p$ = 0.033) according to multiple linear regression adjusted for baseline cognitive parameters, age and sex.

No other significant effects were found.

**Conclusions:** SDB is associated with cognitive deficits in short- and long-term visual memory and executive functions at acute stroke. While SDB does not seem to affect the evolution of cognitive functioning from acute to subacute stroke, SDB treatment from acute to subacute stroke might help to reverse SDB-related deficits in short-term visual memory.

**Disclosure**: No

## O081/P418 | Comparison of novel electrophysiological biomarkers and circulating cardiac biomarkers on all-cause mortality in ASAP epidemiological cohort

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**Objectives/introduction:** The apnoea-hypopnea index (AHI) is used to assess the severity of obstructive sleep apnoea (OSA) despite being poorly associated with adverse outcomes in OSA patients. Novel electrophysiological biomarkers (EPB) such as desaturation parameters have been suggested as an alternative and have been reported to be better at predicting cardiovascular mortality and incidence heart failure. Circulating cardiovascular biomarkers (CCB) are associated with increased EPB in some but not all studies. However, CCBs remain strong predictors of mortality and cardiovascular disease in the general population.

**Aim:** To detect the incidence of all-cause mortality after a median of 13.8 years follow-up in individuals with OSA and to assess the ability of CCB and EPB to predict all-cause mortality.

**Methods:** Polysomnography and CCB analyses (cardiac troponin I (cTnI) and T (cTnT)) were conducted in 535 participants in the Akershus Sleep Apnea study (ASAP) between 2006 and 2008. EPBs evaluated were the AHI, oxygen desaturation index (ODI), desaturation duration (DesDur) and desaturation severity (DesSev). Cox regression was used for survival analysis. Comparison of EPBs and CCBs in how well these parameters predicted all-cause mortality was assessed by the area under the curve (AUC). Data on death was retrieved from patient journals.

**Results:** Forty participants reached the endpoint of all-cause mortality, showing significant difference ($p < 0.01$) at baseline in terms of age, CAD, hypertension, diabetes mellitus, systolic blood pressure, AHI, ODI, SpO2, DesDur, DesSev, cTnI and cTnT, when compared to the subjects who did not reach the endpoint. AHI had a hazard ratio (HR) of 1.01 [95% Confidence interval [CI], 0.99, 1.02]; ODI 1.01 (0.99, 1.03); DesDur 1.02 [0.99, 1.04]; DesSev 1.35 [0.96, 1.89], cTnI 1.64 [1.16, 2.31], $p = 0.005$, cTnT 1.67 [1.00, 2.78)], $p = 0.048$ for all-cause mortality after adjusting for age and gender. Although AUC of cTnI 0.75 was higher than AHI 0.65, DesDur 0.68 and DesSev 0.68, this difference was not statistically significant.

**Conclusion:** Although all biomarkers were significantly higher in participants who reached the endpoint of all-cause mortality, only cTnI and cTnT were associated with increased risk after adjusting for age and gender. There was no difference in the predictive powers of the biomarkers evaluated.

**Disclosure**: No

## O154/P419 | Pitolisant long term effect in sleepy obstructive sleep apnea patients without cpap

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**Objectives:** Pitolisant is a histamine H3-receptor antagonist/inverse agonist waking agent reducing sleepiness in narcolepsy. HAROSA2 1 year study evaluated Pitolisant 20 mg/d (P) efficacy and safety on excessive daytime sleepiness (EDS) in moderate to severe obstructive sleep apnea patients (OSA) refusing CPAP.

**Methods:** 2 periods were defined in HAROSA2: a 12 weeks double blind period (DB) comparing P vs placebo (pl) ($n = 268$) and then was proposed a 40 weeks open label period (OL) with *P* ($n = 236$). The primary criteria was the Epworth sleep scale (ESS) change and the main secondary critria were sleep latency OSleR test (OSL), Pichot fatigue score (PF) and safety.

**Results:** After 1 year, in patients with *P* during DB, we observed an additional ESS reduction $-1.6 \pm 3.4$, an increase of OSL and an improvement of PF $-1.4 \pm 5.9$ during OL. In patients with pl during DB and *P* during PO, we observed an ESS reduction $-5.2 \pm 5.4$, an increase of sleep latency and improvement of PF$-2.9 \pm 6.2$. Most frequent side effects were headaches, insomnia, nausea, vertigo without cardiovascular impact observed.

**Conclusion:** After 1 year, OSA patients without CPAP presenting EDS treated with Pitolisant during DB were improved during OL on ESS,

OSL and PF: Pitolisant efficacy was maintained during 1 year. OSA Patients without CPAP presenting EDS with placebo during DB, then treated with Pitolisant (OL) were improved with a similar ESS reduction. Pitolisant showed a favourable benefit risk balance to manage EDSr in OSA patients refusing of not tolerating CPAP.

**Disclosure**: Yes

**Conflict of Interest statement:** Investigateurs: Dauvilliers, Verbraecken, Partinen, Hedner, Georgiev, Tiholov, Tamisier, Lévy, Pépin Bioprojet: Lecomte, Lecomte, Schwartz

## O155/P420 | Evaluation of sleep-related respiratory events in a continuous large U.S. Sample by home-based under-mattress monitoring devices

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**Objectives/Introduction:** Population studies have estimated the prevalence of sleep-related respiratory events characteristic of obstructive sleep apnea (OSA) and reported night-to-night variability in OSA severity, but these have been constrained by the inability to obtain continuous nightly data on a large scale. The current study is the largest to date for the evaluation of the prevalence and night-to-night variability of these events.

**Methods:** Sleep-disordered breathing was analyzed by a commercially available home monitoring device (Sleeptracker-AI Monitor, Fullpower Technologies Inc., California, USA). The device passively monitors sleep using piezo-electric sensors. Validated sleep and respiratory parameters were derived from device data. The de-identified data were analyzed, following review and exemption of the study (#57681) from Stanford University's IRB. Data were reviewed from April 1, 2021 to March 3, 2022, in 76,769 individuals with 14,296,394 recorded nights. Individuals with at least 300 nights of recordings were included in the analytic dataset.

**Results:** A total of 18,252 individuals (8,592 men, 49.4 ± 13.5 years; 7,336 women, 48.9 ± 13.1 years; 2,324 no gender provided, 49.9 ± 14.5 years) with 5,846,745 recorded nights met the inclusion criterion. Averaged across pairs of consecutive nights, test-retest for OSA severity showed (first-night prevalence, second-night agreement percentage [confidence interval]): mild 16.6% [16.0,17.2], 53.1% [51.1,55.2]; moderate 4.3% [3.9,4.6], 44.6% [40.6,48.7]; severe 1.8% [1.6,2.0], 63.2% [56.9,69.2]. These degrees of agreement are consistent with those previously reported. Averaged across weeks, 12.4% [11.7,13.0] of individuals analyzed met severity criteria for moderate-to-severe OSA (AHI≥15) at least one night out of seven, and we found that the following proportions of such individuals experienced AHI≥15 per given number of nights: one 30.6% [28.1,33.3]; two 15.6% [13.7,17.8]; three 11.1% [9.5,13.1]; four 8.9% [7.4,10.6]; five 8.0% [6.6,9.7]; six 8.5% [7.1,10.3]; and seven 17.0% [15.0,19.2]. Each confidence interval excludes 0%, rejecting the null hypothesis of no AHI variability.

**Conclusions:** The use of a noninvasive in-home monitoring device enables the collection and analysis of sleep and respiratory data on a continuous nightly basis. The prevalence of and variability in sleep-related respiratory events have not been studied in this large of a scale, underscoring the importance of more frequent monitoring in accurately diagnosing OSA and its severity.

**Disclosure**: Yes

**Conflict of Interest statement:** Clete Kushida, Jennifer Zitser Koren, and Feihong Ding have no potential conflicts of funding to disclose and did not receive funding for this research. Anil Rama is a Medical Advisory Board Member for Fullpower Technologies Inc. and has not received any compensation from this company. Andrew Cotton-Clay, Susan Baron, Laura Fava, Venkat Easwar, Arthur Kin solving, and Philippe Kahn are employed by Fullpower Technologies Inc., the manufacturer of the device studied, and own stock and/or stock options in the company.

## O156/P421 | Real-world impact of continuous positive airway pressure on sleepiness in patients with obstructive sleep apnoea in a National Registry

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**Objectives/Introduction**: Excessive daytime sleepiness (EDS) persists in some patients with obstructive sleep apnoea (OSA) despite continuous positive airway pressure (CPAP) treatment. This study aimed to identify real-world impacts of CPAP on EDS in patients with OSA.

**Methods**: Data from the Danish National Patient Registry were analysed. Inclusion criteria were OSA diagnosis between 1994–2016, and Epworth Sleepiness Scale (ESS) scores and apnoea-hypopnoea index (AHI) recorded before beginning CPAP therapy (baseline) and following 1–13 months of CPAP therapy. Patients were excluded if CPAP adherence was unknown. Patients were categorised by ESS score as no EDS (≤10), mild EDS (11–12), moderate EDS (13–15), and severe EDS (≥16).

**Results**: Among 1174 eligible patients (mean ± SD age, 57 ± 12 years; 75.5% male), 692 had no EDS, 155 had mild EDS, 164 had moderate EDS, and 163 had severe EDS at baseline. Overall, 13% and 9.5% of patients used sedatives before and during CPAP treatment, respectively; few used stimulants. During CPAP treatment, 52.5% of patients were CPAP-adherent (use > 4 h/night) on ≥70% of nights. Mean ± SD AHI at baseline was 29.0 ± 24.4 overall; means ranged from 25.2 (no EDS) to 37.3 (severe EDS); after starting CPAP, mean AHI was ≤4.1 for all groups. Mean ± SD ESS score at baseline was 9.5 ± 5.2 overall, and 5.9 ± 3.0, 11.5 ± 0.5, 14.0 ± 0.8, and 18.2 ± 2.0 for the no-EDS, mild-EDS, moderate-EDS, and severe-EDS groups, respectively. At follow-up, mean ± SD changes in ESS score were −3.1 ± 5.1 overall, and −0.8 ± 3.7, −4.0 ± 4.1, −6.4 ± 4.0, and −8.8 ± 5.5 for the no-EDS, mild-EDS, moderate-EDS, and severe-EDS groups,

respectively. Across all groups, mean ESS scores following CPAP treatment were in the normal range (≤10). 76% of patients in the mild-EDS group, 78% in the moderate-EDS group, and 60% in the severe-EDS group achieved ESS scores in the normal range. Furthermore, 17% of the severe-EDS group remained severely sleepy.

**Conclusions**: EDS before CPAP was common among this cohort of patients with OSA. For most patients, ESS scores normalised after CPAP therapy. Patients with severe EDS improved the most, but EDS persisted in a subgroup of patients.

**Disclosure**: Yes

**Conflict of Interest statement: Funding statement:** This study was funded by Jazz Pharmaceuticals.

**Conflicts of interest**: P Jennum, J Kjellberg and R Ibsen have nothing to disclose.

**G Carls** is a consultant to Jazz Pharmaceuticals.

**S Mettam** is an employee of Jazz Pharmaceuticals who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc.

## O157/P422 | Physiological characteristics of obstructive sleep apnea symptom subtypes across international sleep centers

**B. Keenan**[1], N. Jafari[1], A.J. Hirsch Allen[2], P. de Chazal[3,4], N.-h. Chen[5], P. Cistulli[4], T. Gislason[6], F. Han[7], Q.Y. Li[8], N. McArdle[9], J. Mindel[10], R. Schwab[1], B. Singh[9], K. Sutherland[4], N. Ayas[2], T. Penzel[11], U. Magalang[10], M. Younes[12,13], D. Mazzotti[14,15], A. Pack[1], Sleep Apnea Global Interdisciplinary Consortium (SAGIC)

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**Objectives/introduction:** Studies have identified reproducible symptom-based subtypes of obstructive sleep apnea (OSA) with different cardiovascular outcomes, including patients with disturbed sleep, excessive sleepiness, and minimal symptoms. Prior data showed similar apnea-hypopnea indices (AHI) across subtypes, but other objective physiological characteristics have not been comprehensively compared.

**Methods:** Participants from the Sleep Apnea Global Interdisciplinary Consortium (SAGIC) with moderate-severe OSA (AHI ≥ 15) were included. Traditional and novel physiological traits were compared among *Disturbed Sleep*, *Minimally Symptomatic*, and *Excessively Sleepy* subtypes using analysis of covariance (ANCOVA) adjusted for age, sex, BMI and race/ethnicity. Measures included AHI and other respiratory event indices, oxygen characteristics, sleep/wake amounts, electroencephalogram (EEG) spectral characteristics, including metrics related to the odds ratio product (ORP; a validated index of sleep depth ranging from 0.0 [deep sleep] to 2.5 [full wakefulness]), arousal intensity, and heart rate response to arousal. A Hochberg step-up procedure was used to control for multiple comparisons.

**Results:** 638 moderate-severe OSA patients (45.6 ± 26.8 events/h) were included. The cohort was middle aged (51.9 ± 13.8 years), obese (BMI = 32.7 ± 8.0 kg/m$^2$), predominantly males (71.8%), and 41.7% White, 27.0% Asian, 14.9% Central/South American, 5.2% African/African American, and 11.3% Other race/ethnicity. Overall, 112 (17.6%) had the *Disturbed Sleep* subtype, 245 (38.4%) were *Excessively Sleepy*, and 281 (44.0%) were *Minimally Symptomatic*. The *Disturbed Sleep* subtype demonstrated physiological differences reflective of increased wakefulness (more wake time [ANCOVA $p = 0.002$] and wake after sleep onset [$p = 0.0005$]), higher beta frequency EEG power (14.33–20.0 Hz [$p = 0.007$] and 20.33–35.0 Hz [$p = 0.0002$]), and less deep sleep (higher average [$p = 0.0002$] and wake-specific [$p = 0.002$] ORP, less time with ORP from 0.50–0.75 [$p = 0.0003$] and 0.75–1.00 [$p = 0.004$], and more from 2.25–2.50 [$p = 0.0002$]). There were few differences between the *Excessively Sleepy* and *Minimally Symptomatic* subtypes; *Excessively Sleepy* patients had less wake after sleep onset ($p = 0.020$).

**Conclusions:** Differences in specific physiological characteristics, including ORP-related traits, were observed among symptom subtypes. Results demonstrate that differences in objective physiological traits characterize the *Disturbed Sleep* subtype. The absence of physiological differences (including measures of sleep deficiency) between the *Excessively Sleepy* and *Minimally Symptomatic* subtypes was unexpected. Future investigations into underlying molecular causes of the *Excessively Sleepy* subtype are warranted.

**Disclosure**: Yes

**Conflict of Interest statement:** The authors declare no conflicts of interest with respect to the present abstract. This work was supported by the National Institutes of Health (NIH) grant P01 HL094307.

## O158/P423 | Pitolisant long term effect in sleepy obstructive sleep apnea patients with CPAP

**J.-L. Pépin**[1], O. Georgiev[2], R. Tiholov[3], V. Attali[4], J. Verbraecken[5], B. Buyse[6], R. Tamisier[1], P. Lévy[1], I. Lecomte[7], J.-M. Lecomte[8], J.-C. Schwartz[8], Y. Dauvilliers[9]

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**Objectives:** Pitolisant is a histamine H3-receptor antagonist/inverse agonist waking agent reducing sleepiness in narcolepsy. HAROSA1 1 year study evaluated Pitolisant 20mg/d (P) efficacy and safety on residual excessive daytime sleepiness (rEDS) in obstructive sleep apnea patients (OSA) treated with CPAP with a good compliance.

**Methods:** 2 periods were defined in HAROSA1: a 12 weeks double blind period (DB) comparing P vs placebo (pl) ($n = 244$) and then was proposed a 40 weeks open label period (OL) with *P* ($n = 206$). The primary criteria was the Epworth sleep scale (ESS) change and the main secondary criteria were sleep latency OSIeR test (OSL), Pichot fatigue score (PF) and safety.

**Results:** After 1 year, in patients with *P* during DB, we observed an additional ESS reduction −1.21 ± 3.12, an increase of OSL and an improvement of PF −1.6 ± 5.8 during OL. In patients with pl during DB and *P* during PO, we observed an ESS reduction −4.07 ± 5.29, an increase of sleep latency and improvement of PF−1.2 ± 5.8. Most frequent side effects were headaches, insomnia, nausea, vertigo without cardiovascular impact observed.

**Conclusion:** After 1 year, OSA patients with CPAP and presenting rEDS treated with Pitolisant during DB were improved during OL on ESS, OSL and PF: Pitolisant efficacy was maintained during 1 year. OSA Patients with CPAP presenting rEDS with placebo during DB, then treated with Pitolisant (OL) were improved with a similar ESS reduction. Pitolisant showed a favourable benefit risk balance to manage rEDS in OSA patients with CPAP.

**Disclosure**: Yes

**Conflict of Interest statement:** Investigators: Pépin, Georgiev, Tiholov, Attali, Verbraecken, Buyse, Tamisier, Lévy, Dauvilliers
Bioprojet: Lecomte, Lecomte, Schwartz

## O159/P424 | Smoking disturbs the beneficial effects of continuous positive airway pressure on leptin levels in obstructive sleep apnea syndrome

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**Introduction:** The mechanisms underlying the obstructive sleep apnea syndrome (OSAS) and metabolic syndrome are multifactorial, including demographic features, associated risk factors, or habitual risk factors such as smoking. Smoking worsens OSAS, contributes neuromuscular dysfunction in the upper airways, and disturbs the sleep structure. The beneficial effects of continuous positive airway pressure (CPAP) treatment on metabolic profile, on the other hand, are well-demonstrated in many studies. In this study, we aimed to investigate the interaction effects between smoking and CPAP treatment on metabolic profile in patients with OSAS.

**Methods:** A total of 115 patients with OSAS were consecutively and prospectively enrolled into this study. Demographic data, anthropometric features including body mass index (BMI), neck, waist and hip circumferences, habitual factors including smoking, and polysomnographic data were recorded. Metabolic profile including fasting blood glucose, oral glucose tolerance test (OGTT, at 1$^{st}$ and 2$^{nd}$ h), HOMA index, HbA1c, insulin, total cholesterol level, triglyceride, low-density lipoprotein (LDL), and leptin were measured before and after three-months of CPAP treatment.

**Results:** Study population consisted 72 males (62.6%) and 43 females (37.4%). Sixty-one patients (53.3%) were active-smokers; of which 68.7% were males. The mean age of the study population was 53.4 ± 14.3 years. While the gender distribution was similar between smokers and non-smokers, the mean age of the smokers was lower than those of non-smokers ($p = 0.034$). The anthropometric features were similar between two groups. Polysomnographic data were also similar between smokers and non-smokers, including the mean apnea-hypopnea indices. When the changes in metabolic profile were investigated between two groups following CPAP treatment, leptin levels were either decreased (in 78.6%) or stayed stable (21.4%) in non-smokers, while it decreased (in 46.7%), stayed stable (in 13.3%), but also increased (in 40%) in smokers ($p = 0.029$). The changes in other metabolic parameters did not show significant differences between two groups.

**Conclusion:** We demonstrated that smoking has a detrimental effect on leptin levels in patients with OSAS treatment with CPAP. Considering the preparatory role of smoking in leptin resistance, the interaction effect of smoking on CPAP therapy in OSAS patients may be responsible from ongoing metabolic/hormonal and inflammatory processes and cardiovascular risks.

**Disclosure**: No

## O160/P425 | Multi-night objective assessment of snoring is associated with hypertension

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**Objectives:** Snoring and associated effects of labored breathing against a partially obstructed airway and tissue vibration close to the carotid arteries may be a risk factor for cardiovascular disease particularly stroke events. However, snoring may vary within and between nights and current assessments that predominantly rely on bed-partner reports may not be reliable for evaluating associated cardiovascular risks. This study assessed the prevalence of snoring measured objectively over multiple months, and its association with blood pressure and hypertension.

**Methods:** In-home monitoring, using a validated under mattress sleep analyzer, of 12,287 participants over ~6-months was used to assess the average percentage of estimated total sleep time (TST) spent snoring and the apnea-hypopnea index (AHI). Repeat blood pressure measurements were recorded using a home monitor. Hypertension was defined as mean systolic blood pressure ≥140 mmHg and/or a mean diastolic blood pressure ≥90 mmHg. Associations between mean snoring with hypertension were investigated using logistic regression controlled for age, BMI, and sex. Continuous variables, including AHI, were modelled using cubic spline transformations and odds ratios used to compare 75–5th percentiles (reference).

**Results:** Participants were middle aged (Mean ± SD; 57 ± 12 y) and mainly male (88%). There were 2499 cases (20%) with hypertension. Approximately 29%, 14% and 7% of the study population snored on average more than 10%, 20% and 30% of their TST respectively. A higher proportion of TST spent snoring ($75^{th}$ vs $5^{th}$; 12% vs 0.9%) was associated with a ~1.6-fold increase (OR [95%CI]; 1.62 [1.46, 1.81]) in hypertension prevalence. The effect size of the association between snoring and hypertension was higher in younger adults and not obese people (BMI < 30 kg/m$^2$). The association between snoring duration and hypertension remained significant in participants with no-OSA (AHI < 5 events/h; OR [95%CI], 1.73 [1.35, 2.23]).

**Conclusions:** Novel, objective, multi-night snoring recordings in a large sample indicate that snoring is prevalent and that nightly snoring duration is associated with hypertension. These findings highlight the potential clinical utility of simple, objective, and non-invasive methods of snoring and blood pressure assessments for long-term management of obstructed breathing during sleep and associated hypertension risks.

**Disclosure**: Yes

**Conflict of Interest statement:** Withings provided the data to the study investigators but did not fund the current investigator-initiated study or have any role in the study design or direction other than providing access to data. PE serves as a consultant for Withings. Outside the current study, DJE serves as a consultant for Bayer, Takeda and Invicta Medical and as a scientific advisor for Apnimed. No other authors report financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

## O161/P426 | Outcome of surgery in children with suspected obstructive sleep apnea

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**Objective/introduction:** Most children treated for obstructive sleep disordered breathing (oSDB) are not systematically assessed by polysomnography (PSG) nor by structured quantification of symptoms before surgical treatment (ST). The main objective of this study was to investigate the effect of ST on clinical symptoms and PSG parameters.

**Methods:** Otherwise healthy children aged 2–10 years with oSDB symptoms were selected for adeno-tonsillotomy based upon clinical findings according to current standards of care in Denmark. After inclusion, each child underwent standardized assessment before and 3 months after surgery. This included a PSG, measurement of tonsil size and completion of the Pediatric Sleep Questionnaire –Sleep Related Breathing Disorder (PSQ) to quantify symptom burden. Obstructive sleep apnea (OSA) was defined as an obstructive apnea-hypopnea index (oAHI) ≥ 2/h. Successful treatment was defined as post-surgery oAHI ≤ 5/h, and complete cure as post-surgery oAHI ≤ 2/h.

**Results:** Fifty-two children were included, 27 girls, mean age 5.0 years. Significant improvement in OSA severity was only observed in children with moderate to severe OSA at baseline in whom oAHI decreased from 15.7 to 2.6 ($p = 0.0001$). Treatment success was obtained in 86% and cure was obtained in 42% of children. The PSQ-score was significantly reduced from 0.52 to 0.26. Despite normal baseline PSG in 13 children, ST resulted in significant improvement in PSQ-score with complete symptom resolution (PSQ < 0.33) in 67%. Baseline OSA severity was not correlated to baseline symptom burden nor to the degree of symptom improvement after ST.

**Conclusions:** Significant improvement in OSA severity was only observed in children with moderate-to-severe OSA.

**Disclosure**: No

## O162/P427 | Self-perceived sleep during the maintenance of wakefulness test: How does it predict accidental risk in patients with sleep disorders?

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**Objectives/Introduction:** To determine whether the feeling of having slept or not during the Maintenance of Wakefulness Test (MWT) is associated with the occurrence of self-reported sleep-related traffic near misses and accidents in patients with sleep disorders.

**Methods:** This study was conducted in patients hospitalized in a French sleep center to perform a 4 × 40 min MWT. Relationship between mean sleep latency on the MWT, feeling of having slept or not during MWT trials and sleep-related near misses and accidents reported during the past year was analyzed.

**Results:** 192 patients suffering from OSAS, idiopathic hypersomnia, narcolepsy, restless leg syndrome or insufficient sleep syndrome were included. 165 patients presented no or one misjudgment of feeling of having slept during MWT trials while 27 presented more than two misjudgments. Almost half of the latter (48.1%) reported a sleepiness-related traffic near miss or accident in the past year versus only one third (27.9%) for the former ($p < 0.05$). Multivariate logistic regression showed that patients with more than two misjudgments had a 2.52-fold (95% CI, 1.07–5.95, $p < 0.05$) increase in the risk of reporting a sleepiness-related near miss/accident.

**Conclusions:** Misjudgment in self-perceived sleep during the MWT is associated with the occurrence of self-reported sleepiness-related traffic near misses and accidents in the past year in patients suffering from sleep disorders. Asking about the perception of the occurrence of sleep during the MWT could be used to improve driving risk assessment in addition to sleep latencies.

**Disclosure**: No

## O207/P706 | CPAP adherence prediction – recognizing the role of the oxygen desaturation curve

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**Objectives/Introduction:** The search for factors predisposing to continuous positive airway pressure (CPAP) adherence remains inconsistent. Therefore, we aimed to investigate the role of oxygen desaturation expressed as the slope of the oxygen desaturation curve (Slope Index, SI) in short-term CPAP adherence prediction and possible cut-off values of SI in distinguishing good and poor CPAP adherers.

**Methods:** A retrospective study was performed on 70 CPAP-treated patients with severe obstructive sleep apnea (OSA). SI was calculated as the averaged quotient of difference between blood oxygen saturation level before and after the obstructive apnea ($\Delta SpO_2$) and the event duration throughout the night. Apnea-Hypopnea Index (AHI) was defined as a sum of apneas and hypopneas per h of sleep. Good short-term CPAP adherence was defined as CPAP usage for ≥4 h/night on ≥70% of nights during first three months of therapy.

**Results:** Following logistic regression ($R^2 = 16.7\%$; $p = 0.010$), a lower SI was a predictor of good CPAP adherence during first three months of CPAP therapy (OR = 0.004; $p = 0.019$). As a predictor of good CPAP adherence during initial therapy, SI achieved AUC value of 0.650 ($p = 0.032$) with the highest predictive value based on Youden index for 0.465 cut-off. The AUC value for AHI in prediction of good CPAP adherence was not significant ($p = 0.228$). Using the cut-off SI value of 0.465, patients were classified into the group with SI below ($n = 51$) and above 0.465 ($n = 19$). During first three months of therapy, average CPAP usage hours, percentage of nights with CPAP usage and nights with CPAP usage ≥4 h were significantly higher in the group with SI below 0.465 ($p < 0.001$, $p = 0.042$ and $p < 0.001$, respectively).

**Conclusion:** Patients with a steeper slope of the oxygen desaturation curve were identified as more likely to have poor CPAP adherence following therapy onset. SI might be a successful tool in recognizing patients with severe OSA at risk for poor short-term CPAP adherence.

**Disclosure**: No

## O208/P707 | Backscattered ultrasound imaging of the genioglossus muscle as a biomarker of OSA severity in normal BMI versus overweight-obese subjects

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**Objectives/Introduction**: A non-invasive and reliable method of assessing upper airway muscle remains important in understanding the pathophysiology and treatment outcome for obstructive sleep apnea (OSA). Imaging studies with MRI or CT, or awake and sedation endoscopy, have been used to study upper airway muscle position and collapsibility. However, they are not practical for routine clinical implementation. Ultrasound is an appropriate alternative.

Backscattered ultrasound imaging (BUI) measuring tissue anisotropy and heterogeneity on a micro-cellular level has been used in other areas of medicine with similar unmet needs. In this study, we examine the genioglossus (GG) muscle BUI parameters to assess its utility as a biomarker of OSA severity.

**Methods**: 80 subjects (18 female) with mean age of 38.7 ± 12.8, mean BMI of 26.6 ± 4.9, and mean AHI of 17.6 ± 16.5 were consented from the Stanford Sleep Surgery Clinic from July 2020 to January 2022. All subjects underwent attended or home sleep study. 36 subjects have normal BMI, and 44 are overweight (26) or obese (12). Ultrasound radio-frequency data of the upper airway was acquired through standardized submental probe performing a 30-degree scan (15 degrees above and below the Hyoid to external acoustic meatus plane). Echogenicity and BUI parameters along the GG within scan range were assessed. BUI parameters and AHI correlations were performed using nonparametric Mann-Whitney tests, and logistic regression modeling performed using forward method between normal BMI and overweight-obese subjects.

**Results**: In the normal BMI group, BUI signal of the posterior GG muscle is significantly correlated with AHI ($p = 0.0099$). In the overweight-obese group, GG mid-section was significantly correlated with AHI ($p = 0.0095$). In the normal BMI group, BUI of GG independently estimates OSA risk with AUROC reaching 0.835 (95%CI 0.673 to 0.937). BMI, age, and BUI of GG combined estimate OSA risk in the overweight-obese group with AUROC reaching 0.881(95%CI: 0.748 to 0.959).

**Conclusions**: In overweight-obese subjects, BUI of the GG combined with BMI and age predicts severity of disease. In normal BMI subjects, BUI of the GG independently predicts disease severity. BUI parameters of the GG may be useful as a biomarker of OSA severity.

**Disclosure**: No

## O209/P708 | Daytime sleepiness, but not snoring and breathing cessations, was predictive of all-cause mortality in older adults

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**Objective:** To determine if self-reported symptoms of obstructive sleep apnoea (OSA) were predictive of increased all-cause mortality in older adults.

**Methods:** A random sample of all adults aged 71-73 years living in Bergen, Norway in 1997-98, were invited. Participants (1800, 51.6% men, response rate 59%) completed a questionnaire that included questions on snoring, breathing cessations, and daytime sleepiness. The optional answers to these questions were "never", "seldom", "sometimes", "often", and "always". Participants who answered either "often" or "always" were considered positive for the single symptom in question, whereas participants who responded either "sometimes", "often", or "always" on all three items were classified as "OSA cases". These data were merged with data from the Norwegian Cause of Death registry, containing data on all deaths that had occurred by the end of 2014. Crude and multivariate analyses with all-cause mortality as the dependent variable were done for each of the three symptoms and "OSA cases", using survival analyses cox regression to further explore if symptoms of OSA increase mortality. All models were adjusted for age, sex, waist-hip ratio, and smoking habits.

**Results:** The respective prevalence's of snoring, breathing cessations, daytime sleepiness and "OSA cases" were 15.6%, 3.9%, 9.7%, and 3.6%. A total of 876 (48.7%) of the 1800 participants had died by the end of 2014. In crude bivariate analyses, neither self-reported snoring (hazard ratio [HR] 0.97 [0.8, 1.2]), breathing cessations (HR 1.05 [0.7, 1.6]), nor "OSA cases" (HR 1.25 [0.9, 1.8]) were associated with mortality, but daytime sleepiness was associated with increased mortality (HR 1.45 [1.1, 1.8]). The adjusted cox regression analyses yielded similar results, with snoring (HR 0.85 [0.7, 1.0]), breathing cessations (HR 0.91 [0.6, 1.4]), and "OSA cases" (HR 0.87 [0.7, 1.5]) not being associated with increased mortality risk, but for daytime sleepiness a significant association was found with a HR of 1.51 (1.2, 1.9).

**Conclusions:** In this study, daytime sleepiness conferred an independent 50% increased risk of mortality to older adults, but for snoring, breathing cessations and "OSA cases" no such association was found.

**Disclosure**: No

## O211/P709 | Interventions to improve positive airway pressure therapy adherence in obstructive-sleep apnea patients: a meta-analysis

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**Objectives/Introduction:** Literature suggests poor obstructive sleep apnea (OSA) patient adherence to positive airway pressure therapy (PAP). Specifically, PAP adherence, ranging between 23% and 89%, lowers the effectiveness of treatment and increases the risk of mortality. Our meta-analysis aims to quantify the efficacy of different interventions (Psychoeducation, Behavioral, and Cognitive-Behavioral interventions) on PAP adherence in OSA patients.

**Methods:** A systematic review of the literature was performed by three independent researchers in Pubmed, Psychinfo, Cinhal, Embase, Scopus, and Medline up to April 2021. We include Randomized Controlled Trial (RCT) in OSA patients, with different interventions (Psychoeducation, Behavioral and Cognitive-Behavioral) aimed at improving positive airway pressure adherence. The publication bias has been evaluated qualitatively following Cochrane Collaboration guidelines. Abstracts conferences have been searched in special issues of the most relevant journals in the field. A random-effects meta-analysis model was implemented evaluating PAP adherence (i.e., mean

of PAP usage in hours per night) as the principal outcome. The follow-up duration was used as a covariate in the model.

**Results:** 47 RCT met the inclusion criteria (N intervention = 3571; N controls = 3537). 10 RCT proposed Behavioral (BEH) intervention in 1462 OSA patients compared with 1493 controls. In the BEH subsample of studies, analyses showed adherence improvement with a medium effect (RE model $d = 0.44$, CI 0.20–0.67). Psychoeducational (EDU) interventions were planned in 32 RCT studies (N intervention = 1878; N controls = 1814). The results suggested a medium EDU effect on PAP adherence (RE model $d = 0.56$, CI 0.18-0.93). Finally, Cognitive-Behavioral interventions (CBT) were administered in 5 RCT studies (N intervention = 231; N controls = 230), and the results displayed a medium-to-large effect (RE model $d = 0.69$, CI 0.16–1.22). No effect of follow-up duration was found in all three models.

**Conclusions:** This meta-analysis reports evidence from 47 RCT studies. Medium-to-large positive effects of Psychoeducation, Behavioral, and Cognitive-Behavioral interventions on PAP adherence in OSA patients were found. Among all interventions, CBT showed the largest effect in comparison to other approaches.

**Disclosure**: No

## O212/P710 | Pitolisant efficacy in excessive daytime sleepiness for patients with obstructive sleep apnea

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**Objectives:** Pitolisant a Histamin H3-receptor inverse agonist waking agent for Excessive Daytime Sleepines (EDS) treatment in narcolepsy showed efficacy on EDS in Obstructive Sleep Apnea (OSA) patients with EDS treated respectively with and without Continuous Positive Airway Pressure (CPAP). Its efficacy and safety at 20 mg/day was evaluated through an Individual patient data meta-analysis vs placebo.

**Methods:** Epworth Sleep Scale (ESS) and Oxford Sleep Resistance (Osler) tests were co-primary endpoints tested at 0.025 significance and Fatigue (Pichot Scale) was secondary.

**Results:** A significant mean ESS reduction of -3.06([95%CI −4.1,−2.02], $p < 0.001$) was found with Pitolisant versus placebo and 81% more patients decreased final ESS to less than 10 (RR = 1.81 [95%CI 1.36, 2.39], $p < 0.001$). The Osler Final/Baseline was also 18% better (ratio = 1.18[95%CI 1.02, 1.35], $p = 0.022$). A clinically meaningful EDS effect of Pitolisant measured by the aggregate Z-score on ESS and Osler was 0.71([0.46, 0.97], $p < 0.001$). Finally, a significant mean Pichot Fatigue reduction of −1.23([−2.29,0.18], $p = 0.022$) was found. These effects were shown invariant across various subgroups of the population (age, gender, work conditions). Finally these effects were not impacted as to whether or not CPAP was used. Side effect incidence was similar in both groups.

**Conclusions:** These results confirm pitolisant efficacy on EDS and Fatigue symptoms in sleepy OSA patients versus placebo, evaluated by the ESS, Osler, EDS Z-score and Pichot Fatigue, irrespective of CPAP use.

**Disclosure**: Yes

**Conflict of Interest statement:** Bioprojet sponsored this analysis. CC is employee of bioprojet pharma. JLP, YD, VA, were investigators, PL received honoraria from bioprojet.

## O213/P711 | Isolated nocturnal hypoventilation in treated sleep apnea patients

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**Objectives:** The current European classification of obesity hypoventilation contains the concept of nocturnal hypoventilation with a normal daytime blood gas. The occurrence of isolated nocturnal hypoventilation (INH) in sleep apnea patient on treatment is unknown. Our objective was to study the occurrence, clinical determinants and treatment outcome of INH in sleep apnea patients with persistent daytime complaints despite seemingly adequate positive airway pressure (PAP) therapy referred to a tertiary sleep clinic.

**Methods:** A retrospective single-center study was conducted in 96 known sleep apnea patients (80% obstructive) with persistent daytime complaints despite adequate PAP therapy. Patients underwent clinical polysomnography (PSG) with simultaneous transcutaneous pCO2 (TcpCO2) measurement and additional daytime capillary blood gas measurement. Isolated nocturnal hypercapnia was defined as ≥5% total sleep time (TST) TcpCO2 > 50 mmHg with a normal daytime blood gas. Patients with any form of hypercapnia and isolated nocturnal hypercapnia were compared to normocapnic patients. The subgroups were compared on demographic and anthropometric patient characteristics, PSG parameters, subjective complaints, medication use and comorbidities.

**Results:** In this sample, the occurrence of any form of hypercapnia and isolated nocturnal hypercapnia was 47% and 24%, respectively. Patients with isolated nocturnal hypercapnia have on average a higher oxygen desaturation index (ODI) and TST $SpO_2$ < 90%and less N3 sleep as compared with normocapnic patients. Demographic and anthropometric patient characteristics, subjective complaints and comorbidities do not differ between the subgroups. Opioid use (OR = 5,706, $p = 0.042$) and TST SpO2 < 90% (OR = 1,148, $p = 0.044$) are predictors of hypercapnia. Under the diagnosis INH patients are more often treated with bilevel PAP therapy (BPAP) than

normocapnic patients. Also patients with isolated nocturnal hypercapnia subjectively experienced greater improvement in symptoms after change to BPAP.

**Conclusions:** Isolated nocturnal hypercapnia is frequently found in our sample of sleep apnea patient on PAP treatment with persistent daytime complaints. Investigation of TcPCO2 lead to change in diagnosis and treatment and improved subjective outcome. Further prospective research is recommended to gain a better understanding of the etiology, diagnosis, treatment and prognosis of isolated nocturnal hypercapnia.

**Disclosure**: No

## O214/P712 | Shared decision making: a novel approach to personalized treatment in obstructive sleep apnea data from the Akershus sleep apnea clinical cohort

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**Introduction:** (i) To describe a novel approach to personalized treatment by shared decision making (SDM) in obstructive sleep apnea (OSA) discharge consultations

(ii) to describe correlation between patient and observer-based evaluations of SDM and (iii) to describe treatment adherence.

**Methods:** Consecutive patients referred to the otorhinolaryngology department at Akershus University Hospital with suspected OSA between 2015 and 2016 participated. One hundred and sixty-four patients were diagnosed with OSA. Patients with body mass index > 30 were oversampled. Four communication trained doctors participated. Patients could by protocol choose no treatment, primary surgery (if indication), self-managed 10% weight reduction and/or positive airway pressure (PAP) treatment. SDM was evaluated by modified content analysis and by the CollaboRATE self-report questionnaire and the "Observer OPTION5" rating scale. PAP treatment adherence and weight reduction was assessed by interview at six year follow-up.

**Results:** Eighteen consultations were video filmed. The content analysis revealed that the patient perspectives only briefly were explored. PAP was chosen by 17 of 18 patients. Median CollaboRATE questionnaire score was 29 (26, 30). Mean OPTION5 score was 65.6 (SD 6.6, range 55–80). The correlation between SDM assessed by CollaboRATE self-report and by the "Observer OPTION5" rating scale was low (Pearson's $r = 0.09$). At follow up, 11 patients (64.7%) were PAP adherent, and no one achieved 10% weight loss.

**Conclusions:** SDM is a promising tool in the clinical meeting with the OSA patient. However, by not exploring the patient perspective, clinicians potentially lost valuable information. The relation between SDM assessed by self-report and by the observer rating scale was weak and may indicate assessment of different constructs. PAP adherence was good, whereas our results indicate that self-managed weight reduction without support was not a feasible treatment option.

**Disclosure**: No

## O215/P713 | OSAREDS study preliminary results: Eds in Italian patients with OSAS and REDS after CPAP treatment

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**Introduction:** in obstructive sleep apnea (OSA) patients prevalence of excessive daytime sleepiness (EDS) at diagnosis and of residual EDS (rEDS) after treatment vary among studies.

**Objective:** *OSA*-related *R*esidual *EDS* prevalence in Italian patients (OSAREDS) study was aimed at assessing the prevalence of EDS and of rEDS (Epworth Sleepiness Scale [ESS] score > 10), after continuous positive airway pressure (CPAP) treatment, in OSA Syndrome (OSAS).

**Methods:** The study retrospectively analyzed characteristics, symptoms, treatments and compliance to CPAP of patients referred to 7 Italian sleep centres with OSA's symptoms.

**Results:** Among 2432 patients included in an interim analysis, 861 (males: 74.2%, mean age ± SD: 56.5 ± 8.8 y, BMI: 31.3 ± 4.8 kg/m$^2$) were evaluated at baseline and after 3–12 months (median 9.6 months) of CPAP treatment. In this subgroup, before CPAP, AHI (mean ± SD) was 35.9 ± 25.8, ESS score (mean ± SD) was 8.8 ± 5.0 and main symptoms' prevalences were: EDS 36.5%, snoring 97.1%, fatigue 31.1% and insomnia 13.5%. Mean symptoms duration was 61 ± 41.6 months. Comorbidities frequencies were: systemic hypertension 59.2%, type 2 diabetes 16.0%, arrythmias 6.7%, and asthma 5.5%. CPAP was accepted by 98.7% of patients and 93.7% were adherent at follow-up. Mean CPAP use was 5.4 ± 2.6 h/night for 77.7% of the nights and average therapeutic pressure was 8.3 ± 3.7 cm$H_2O$. At follow-up visit, mean AHI was 6.1 ± 7.2/h and mean ESS score was 4.6 ± 3.7 ($p < 0.01$ by *t*-test). Prevalence of rEDS decreased to 6.6% (95% CI 5.0-8.3, $p < 0.01$) in the whole population and was 18% in OSA patients that had EDS at baseline. Prevalence of snoring decreased to 12% and those of fatigue and insomnia to 10.5% and 5.6%, respectively ($p < 0.0001$ for all).

**Conclusions:** The interim analysis of the OSAREDS study found that CPAP reduced OSA's symptoms prevalence, but rEDS, snoring, fatigue and insomnia still affect variable percentages of patients after 3–12 months of treatment.

**Disclosure**: Yes

**Conflict of Interest statement:** Consultancy for Bioprojet Italia

## 15: SLEEP DISORDERS - CIRCADIAN RHYTHMS

### O178/P717 | Eveningness is associated with coronary artery calcification in a middle-aged swedish population

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**Introduction:** Coronary artery calcification (CAC) is a widely used imaging biomarker of subclinical atherosclerosis, but its relationship to sleep timing is not well studied. We have recently demonstrated that extreme evening chronotype is associated with increased cardiovascular risk.(1) We hypothesize that chronotype is associated with CAC independent of traditional cardiovascular risk factors in the Swedish Cardiopulmonary bioImage Study (SCAPIS) pilot cohort.

**Methods:** Residents aged 50–64 years from two areas of high and low socioeconomic status of Gothenburg, Sweden were randomly recruited and underwent extensive examination with imaging and functional testing. 767 participants (48% male, 58 ± 4 years) were included in this cross-sectional analysis. CAC was assessed in non-contrast computed tomography of the coronary arteries and the Agatston method was used to calculate CAC score, a measure of calcium volume and density. Significant CAC was defined as a CAC score ≥10. 10-year risk of cardiovascular disease was assessed by the SCORE2 algorithm based on age, gender, smoking status, systolic blood pressure, and non-HDL cholesterol. Self-assessed chronotype was classified as extreme morning, moderate morning, intermediate, moderate evening, or extreme evening.

**Results:** Significant CAC was present in 30% of the cohort and was associated with increased SCORE2 (7.1 ± 3.1% vs. 4.8 ± 2.4%, $p < 0.001$). CAC prevalence increased from extreme morning to extreme evening type (23%, 28%, 30%, 29%, 42% respectively, $p = 0.015$). In a generalized linear logistic regression model controlling for socioeconomic status, accelerometer-assessed physical activity, sleep duration, SCORE2, and comorbidities, extreme evening chronotype was independently associated with increased CAC prevalence compared to extreme morning type (OR 1.89, [95%CI 1.04-3.37], $p = 0.038$). SCORE2 was also found to be a significant mediator of the relationship between chronotype and CAC prevalence in a mediation analysis.

**Conclusion:** This is the first study demonstrating an independent association between CAC and chronotype. Our findings suggest that circadian factors play an important role in the development of atherosclerosis in addition to traditional risk factors (SCORE2). Sleep timing should be considered in the development of prevention strategies.

(1) Kobayashi Frisk et al. Eveningness is associated with sedentary behavior and increased 10-year risk of cardiovascular disease – the SCAPIS pilot cohort. Sci Rep. In press.

**Disclosure**: No

## 16: SLEEP DISORDERS - INSOMNIA

### O030/P132 | What moderates CBT for insomnia? Findings from a participant-level analysis of 8,549 individuals in 12 randomised controlled trials of digital CBT (Sleepio)

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**Objectives:** To determine moderators of digital CBT (dCBT [Sleepio]) for insomnia by estimating the effects of treatment, with sufficient power, amongst different groups of people using personal demographic and clinical characteristics as moderators.

**Methods:** A collaborative working group was formed with authors from all 12 published RCTs of the fully automated (i.e., without therapist support) dCBT. Authors provided individual participant-level data (IPD) from each RCT. We harmonised demographic and clinical characteristics from 8549 individuals who had been randomised and used robust IPD statistical techniques to evaluate potential moderators. Moderators of insomnia symptom response were assessed using validated measures across all sub-groups. This project was registered in PROSPERO (CRD42019105424).

**Results:** Across the sample (75% female, mean age = 35.4 y; $n$ = 8,549) dCBT had a large effect in favour of dCBT for symptoms of insomnia ($d = -1.02$) with small-to-medium effects for depression ($d = -0.28$) and anxiety ($d = -0.31$) at post-treatment compared with controls. Participant sex, education, and employment status did not moderate insomnia symptoms. For clinical symptoms, those who had greater insomnia severity ($d = -1.18$), a longer duration of symptoms (>1 year, $d$ = -1.47 vs. ≤1 year, $d = -1.10$), with comorbidities ($d = -1.40$ vs. none $d = -1.06$), and who were in a relationship ($d = -1.52$ vs. those who were not, $d = -1.12$) experienced greater benefits with dCBT for insomnia symptoms at post-treatment compared with similar controls. Baseline symptoms of anxiety and depression did not moderate insomnia treatment effects.

**Conclusions:** This may be one of the largest moderation analyses of CBT, and possibly the largest in CBT for insomnia. The study helps answer a longstanding question as to who benefits most from CBT. This fully automated dCBT intervention [Sleepio] was an effective treatment for insomnia across many different groups of patients. We did not find any major contraindication to treatment based on demographic or clinical characteristics of participants. Digital CBT for insomnia was somewhat more effective in people who had more severe insomnia than those with less severe symptoms. These methods and findings generate specific hypotheses for research on moderators of response to CBT in insomnia and further mental health disorders including anxiety and depression.

**Disclosure**: Yes

**Conflict of Interest statement:** CM is employed by Big Health Inc. and is salaried by the company. CE is the Co-Founder and Chief Scientist of Big Health Inc. and is a shareholder. AH is employed by Big Health Inc., is salaried by the company and is a shareholder. RE receives consultancy fees from Big Health Inc. AL held a position at the University of Oxford funded by Big Health Inc. in the past (2015–2018). The digital self-help intervention, Sleepio, was made available to all participants at no cost.

## O031/P133 | Spectral analysis of PSG recordings in insomnia and non-insomnia subjects - new insights in sleep microarchitecture

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**Objective:** To characterise spectral EEG features in subjects with and without insomnia.

**Methods:** Adults with insomnia (4928 PSG recordings) were selected from three datasets: Sleep Heart Health Study (SHHS), Massachusetts General Hospital (MGH) (both via Beacon Datastore™), and Idorsia daridorexant phase 3 studies (untreated subjects). Non-insomnia (control) subjects (3282 PSG recordings) were selected from MGH and SHHS datasets. Subjects taking medications/diagnosed with ongoing illness that would impact sleep studies were excluded.

Delta (1–3 Hz, high amplitude), theta (4–7 Hz), alpha (8–12 Hz), and beta (13–38 Hz, low amplitude) band spectral power of sleep EEGs was estimated using multi-taper spectrograms (2 s window/1 s overlap). Relative power was computed using the sum of these four band powers within the 2 s window as the denominator, and for pairwise band powers. The resulting relative and band power ratios were then aggregated to 30 s epochs and assessed by sleep stages. Analysis was done using a univariate analysis of spectral features via linear mixed-effects regression, incorporating fixed effects (e.g., age, sex, and insomnia/non-insomnia), fixed effects interactions and random effects by site.

**Results:** More recordings were from women (54% of insomnia subjects, 61% of controls). Age distribution was similar between groups. Insomnia subjects had lower mean relative delta power and higher mean relative alpha and theta power in Wake and N1 versus controls ($p < 0.05$). In Wake and N1, insomnia subjects had more variation (standard deviation) in relative alpha power vs controls, and they had less variation of relative delta and beta power in Wake ($p < 0.05$). In REM, insomnia subjects had more variation in relative alpha and delta power whereas mean relative powers did not differ between insomnia subjects and controls. Relative spectral powers in N2 and N3 did not differ.

**Conclusions:** This is one of the largest studies to date to assess EEG spectral patterns in subjects with insomnia, and, after adjusting for multiple confounds, reveals that subjects with insomnia have more alpha and less slow (delta) EEG activity than subjects without insomnia, mainly in Wake and N1 stages. These differences in sleep architecture further support the insomnia hyperarousal model and may provide opportunities for better understanding the physiopathology of insomnia.

**Disclosure**: Yes

**Conflict of Interest statement:** Employee of Idorsia Pharmaceuticals

## O032/P134 | Clinical and cost-effectiveness of nurse-delivered sleep restriction therapy for insomnia in primary care: a pragmatic, multicentre, randomised controlled trial

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**Objectives:** Access to cognitive behavioural therapy for insomnia remains extremely limited. We aimed to establish the clinical and cost-effectiveness of a brief nurse-delivered behavioural intervention for insomnia in primary care.

**Methods:** We did a pragmatic, multicentre, individually randomised, parallel group, superiority trial of sleep restriction therapy (SRT) versus sleep hygiene (SH).Adults with insomnia disorder were recruited from general practice in England and randomised to either four session nurse-delivered SRT (2 in-person sessions, 2 over the phone) or SH booklet. There was no restriction on usual care for both groups. Outcomes were assessed at 3, 6, and 12 months. The primary end-point was self-reported insomnia severity at 6 months measured with the insomnia severity index (ISI). Cost-effectiveness was evaluated from the UK National Health Service and Social Care perspective by using the incremental cost per quality-adjusted life year (QALY). The trial was prospectively registered with the ISRCTN (ISRCTN42499563).

**Results:** Between August 29, 2018 and March 23, 2020 we randomised 642 participants (SRT, $n = 321$; SH, $n = 321$). 580 participants (90.3%) provided data at a minimum of one follow-up time-point. At 6 months post-randomisation, the estimated adjusted mean difference on the ISI was −3.05 (95% CI: −3.83 to −2.28, $p < 0.001$, Cohen's $d = 0.74$), indicating that participants in the SRT arm reported lower insomnia severity compared to SH. Large treatment effects were also found at 3 ($d = 0.95$) and 12 months ($d = 0.72$). Superiority of SRT over SH was evident at 3, 6, and 12 months for self-reported sleep, mental health-related quality of life, depressive symptoms, work productivity impairment, and sleep-related quality of life. Eight participants in each arm experienced serious adverse events but none were judged to be related to intervention. The incremental cost per QALY gained was £1350, giving a 90% probability that SRT is cost-effective at a willingness-to-pay threshold of £20,000.

**Conclusions:** Brief nurse-delivered SRT in primary care is clinically effective for insomnia, safe, and very likely to be cost-effective. Healthcare systems should consider training primary care nurses to treat insomnia in order to increase access to the first-line treatment.

**Disclosure**: Yes

**Conflict of Interest statement:** CAE is co-founder of and shareholder in Big Health Ltd., a company that specialises in the digital delivery of cognitive behavioural therapy for sleep improvement (the Sleepio programme), out with the submitted work. LM is a salaried employee of mementor DE GmbH, a software company specialising in digital sleep intervention, out with the submitted work. All other authors declare no competing interests.

## O033/P135 | Sleep characteristics of london marathon participants

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**Introduction:** Marathon races are more popular than ever, with major events attracting between 20,000 and 40,000 participants. Marathon completion requires sustained cardiovascular effort over multiple h. Sleep health influences cardiovascular performance and plays a key role in injury prevention. Problematically, marathon runners are at heightened risk for poor sleep due largely to training demands. Marathoners, therefore, represent a nontrivial portion of the population that may be at risk for poor sleep due to its relationship with cardiovascular workload. The aim of this investigation was to explore the sleep characteristics among marathoners.

**Methods:** Data were obtained from the 2016 London Marathon participants. Participants completed the Athlete Sleep Screening Questionnaire (ASSQ). Runners were characterized as fast and regular runner based on the good for age qualifying times. ANOVA assessed ASSQ differences across runner ability, gender, and age groups, with MANOVA utilized to assess group differences while controlling for other characteristics.

**Results:** Final sample ($n = 951$) was predominantly regular runners (78.6%), male (64.7%), and 18–39 (65.9%) years old. Female runners reported less total sleep time (TST) ($F(1,949) = 10.1$; $p = 0.002$), with this relationship maintaining when controlling for runner ability and age. Additionally, females reported more sleep maintenance problems, but this relationship was only significant when controlling for runner ability and age ($F(1,941) = 4.08$; $p = 0.04$). Fast runners reported significantly more sleep maintenance problems ($F(1,949) = 4.85$; $p = 0.03$), with this relationship maintaining when controlling for gender and age. Also, significant variance in sleep onset latency (SOL) was observed across age groups, when controlling for gender and runner ability, with a general trend of younger runners having longer SOL (*F*

(7,941) = 2.97; $p = 0.004$). Lastly, 23.7% of participants would have been referred to a sleep physician based on ASSQ score.

**Conclusion:** Gender, runner ability, and age differences influenced TST, WASO, and SOL. Approximately 25% of participants reported sleep characteristics warranting referral to a sleep clinician. These results indicate that sleep health is an important factor for runners and coaches to consider in the overall training program of marathon athletes.

**Disclosure**: No

## O034/P136 | Analysis of predictors of effect in a study of guided Internet-based Cognitive-Behavioral Therapy of Insomnia (ICBT-I)

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**Introduction:** Understanding which factors predict iCBT-I's effectiveness can help referrers to select the target group of patients that benefit most or directly refer patients that are unlikely to benefit from this intervention to a more resource-intensive treatment setting.

**Methods:** This is a post-hoc analysis of a three-arm randomized controlled trial (RCT) comparing the effectiveness of guided internet-based multi-component treatment (MCT), an internet-based guided sleep restriction treatment (ST), and care as usual (CAU) for 104 chronic insomnia patients (Krieger et al., 2019). Demographics (including social and work status, level of education), medical history (use of medication) and baseline scores of sleep quality, dysfunctional beliefs and attitudes about sleep, depressive symptoms, quality of life, personal significance of the sleep problems, and expectations about treatment success were obtained before the intervention. Primary outcome - the insomnia severity index (ISI) was assessed before and after the 8 weeks intervention. Since treatment groups in the RCT proved to be equally effective in reducing ISI, the MCT and ST groups were merged and compared to CAU. The ISI improvement from baseline to posttreatment was the dependent variable to assess the impact of predictors on the negative change in symptom severity over time (prognostic analysis) and response to treatment (predictive analysis). Predictors were analyzed with multiple linear regression models including ISI at baseline and condition (treatment or CAU).

**Results:** Higher education (Std $\beta = 0.88$ score points, $p = 0.033$) and female gender (Std $\beta = 1.65$ for females vs. males, $p = 0.051$) had prognostic value for a better outcome in both arms. Individuals who consumed medications (Std $\beta = -3.81$, $p = 0.059$) and those expecting high therapy success showed better effect in treatment group (Std $\beta = 1.33$, $p = 0.024$). The worst ISI dynamic was in the CAU group participants with the high personal significance of sleep problem (Std $\beta = 0.21$, $p = 0.071$) and those who were divorced (Std $\beta = 7.36$, $p = 0.0036$).

**Conclusions:** Findings indicate that insomnia patients receiving pharmacotherapy for insomnia, and those with a higher success expectancy regarding the intervention profit most of iCBT-I. Results suggest that patients requiring closer medical and/or psychological attention are those that are divorced and those who attribute a high personal relevance to sleep problems.

**Disclosure**: No

## O035/P137 | Positive affect as a mediator of the longitudinal association between night-time insomnia symptoms and C-reactive protein: a four-year follow-up

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**Objectives/Introduction**: Previous evidence suggests that night-time insomnia symptoms (i.e., difficulties in sleep onset and sleep maintenance) may be associated with increased peripheral inflammatory markers, which is involved in the pathophysiology of mental and somatic illness. The mechanisms underlying this association, however, remain largely unknown. In the context of health psychology, a substantial body of literature suggests that positive affect may have favourable impact on immune and inflammatory response and buffer the proinflammatory effects of stress. With this background, the aim of this study was to assess whether subjective sleep disturbance is longitudinally associated with serum high sensitivity C-reactive protein (hs-CRP), an acute-phase protein which is considered a marker of systemic inflammation, and whether this association is mediated by a decrease in positive affect.

**Methods:** We analysed data from the English Longitudinal Study of Ageing (ELSA) across three waves of data collection. Self-reported sleep disturbance was assessed in 2008–2009, (wave 4), positive affect was assessed in 2010–2011 (wave 5), and serum sh-CRP was assessed in 2012–2013 (wave 6). Path analysis (i.e., structural equation modelling) was conducted adjusting for health-related variables including depressive symptoms, cardiovascular disease, body mass index, smoking, and alcohol intake.

**Results:** The sample included 1894 participants aged 64.11 ± 8.02 years, 51% females. The model showed an excellent fit to the data: $\chi 2 = 9.78$ (df = 7, $p > 0.05$); RMSEA = 0.014 (95% CI 0.000 to 0.034); CFI = 0.997; TLI = 0.994; SRMR = 0.014. Path analysis showed a significant direct effect of sleep disturbance to positive affect ($\beta = 0.15$; $p < 0.001$); positive affect directly predicted hs-CRP ($\beta = 0.04$; $p < 0.05$). Lastly, an indirect effect between sleep disturbance to hs-CRP through the mediating role of positive affect emerged ($\beta = 0.006$; $p < 0.05$); bias-corrected bootstrap confirmed the statistical significance of the indirect effect ($p < 0.05$).

**Conclusions:** Findings suggest that sleep onset and sleep maintenance difficulties may influence peripheral inflammation via a decrease in positive affect. Replication studies in clinical populations with

insomnia disorder are warranted. Our study highlights the need to explore the role of positive affectivity in future population-based studies on sleep disorders and health risk.

**Disclosure**: No

## 17: SLEEP DISORDERS - PARASOMNIAS

### O013/P143 | Validation of 3D video automatic analysis to identify rapid eye movement sleep behavior disorder

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**Objectives/Introduction**: Diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) requires video-polysomnography including quantification of REM sleep without atonia and visual inspection of video. Visual video inspection is a time-consuming process. In a previous work (Waser et al., Sleep 2020), we proposed 3D video automatic analysis as a new technology to identify RBD patients based on recognition of short movements (0.1–2 s) in the lower limbs during REM sleep. In this work, we further validated this technology and investigated the benefit of including analysis of movements in the hands and head.

**Methods:** We included 182 patients who underwent video-polysomnography with simultaneous recording of 3D video. Video-polysomnographies were manually scored according to international criteria. Of the included patients, 54 had isolated RBD, 51 sleep-related breathing disorders, 21 restless-legs-syndrome, 20 insomnia, 12 periodic limb movements during sleep without any associated disorder, 6 NREM parasomnia and 19 did not have any relevant sleep disorder. An algorithm was developed to identify movements with duration 0.1–2 s from the 3D video during manually scored REM sleep in the following regions of interest (ROIs): head, hands and lower limbs. For each ROI, features describing the number and length of movements in REM sleep were calculated. With 10-fold-cross-validation, logistic regression models were trained and tested to distinguish RBD from the other patients, by considering (i) head movements only, (ii) hands movements only, (iii) lower limbs movements only, and (iv) head, hands and lower limbs movements. Accuracy, sensitivity and specificity were calculated.

**Results:** The following test accuracy-sensitivity-specificity values were obtained: 75.3%-63.0%-80.5% (head movements only), 70.3%-53.7%-77.3% (hands movements only), 84.6%-83.3%-85.2% (lower limbs movements only), 85.2%-83.3%-85.9% (head, hands and lower limbs movements).

**Conclusions**: Automatic 3D video analysis of lower limb short movements is confirmed as specific and sensitive for identifying RBD. When considering short movements only in the hands and head, the performances were lower than when considering only short lower limb movements. The combination of short movements in the three ROIs led to the highest performances. Therefore, 3D automatic video analysis of short movements in lower limbs, hands and head allow accurate, sensitive and specific identification of RBD patients.

**Disclosure**: Yes

**Conflict of Interest statement:** Study supported by Austrian Science Fund (FWF), project KLI-677 B31. No other relevant conflict of interest to be declared.

### O017/P144 | REM-sleep without atonia as prognostic biomarker in prodromal α-synucleinopathies

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**Objectives:** Isolated REM-sleep behavior disorder (iRBD) is a prodromal state of clinical α-synucleinopathies such as Parkinson's disease and Lewy-body dementia. REM-sleep without atonia (RWA) is the neurophysiologic hallmark in the diagnosis of RBD. Decremental striatal dopamine-transporter-(DaT)-binding has been identified as most reliable progression marker, with DaT-images determined as pathologic indicating short-term risk of pheno conversion in the near future. The aim of this study was to systematically describe DaT-imaging in a large and homogenous sample of patients with iRBD and to determine the correlation of DaT-binding with RWA for the use of RWA as prognostic marker.

**Methods:** 221 clinically suspected patients with RBD underwent three-night video-polysomnography (vPSG) and DaT single-photon-emission computed-tomography (SPECT). Nineteen patients were excluded for technical reasons. Group comparisons were analyzed using mixed linear models.

**Results:** vPSG confirmed RBD in 162 patients (148 iRBD, 14 pheno converted). In 40 patients sleep-related motor behavior was considered unrelated to α-synucleinopathies. Specific DaT-binding ratios (SBR) differed significantly between these three groups, but showed considerable overlap. RWA-metrics correlated significantly with DaT-SPECT-values (e.g., RWA-tonic vs. SBR in most-affected-site: $r = 0.531$; $p < 0.001$), most pronounced tonic RWA vs. right posterior putamen. Time since reported start of RBD symptoms was not correlated with DaT-binding and RWA-scores. Possible confounders like intake of beta-blockers or co-morbid sleep apnea did not weaken correlations. Intake of serotonergic/noradrenergic antidepressants, dopaminergic substances or recent alcohol abuse lowered correlations, suggesting confounding influence.

**Conclusions:** This large single-center study describes measures of RWA and DaT-binding in patients with iRBD to be a continuum in the neurodegenerative process. Overlap between the three patient groups excludes DaT-binding as a precise diagnostic marker. The

continuous and parallel course of DaT-binding ratios and RWA-measures suggests ranges of early, medium and advanced states within prodromal α-synucleinopathies, which may allow to feed-back estimated time until possible conversion (in combination with serial monitoring of other specific biomarkers). RWA may represent the best available progression marker at no additional costs.

**Disclosure**: No

## 18: SLEEP DISORDERS - MOVEMENT DISORDERS

### O016/P151 | Large muscle group movements during sleep in healthy sleepers

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**Introduction:** Large body movements during sleep are often accompanied by sleep stage shifts, arousals, awakenings, respiratory events and autonomic changes, therefore likely having relevant clinical implications. The current American Academy of Sleep Medicine scoring manual (AASM Version-2.6) does not contain clear rules to define and score large body movements during sleep. Recently, a taskforce of the International Restless Legs Syndrome Study Group developed criteria to detect and score large muscle group movements (LMM) during sleep (Ferri et al., Sleep, 2021). Normative values for LMM in adults are not available yet.

**Objectives:** To investigate the prevalence and features of LMM in healthy adult sleepers.

**Methods:** LMM were scored following the published criteria in a cohort of 100 healthy sleepers aged 19–77 years, previously recruited from a representative population sample. All subjects underwent v-PSG according to AASM 2007 standards. The following channels were included for LMM scoring: six EEG signals, four EOG, ECG, chin EMG, both tibialis anterior and flexor digitorum superficialis muscles EMG. LMM indices and duration in total sleep time (TST), NREM, and REM sleep were calculated. Indices were also calculated for LMM occurring alone, in association with arousals, awakenings, or respiratory events.

**Results**: The median LMM index in TST was 6.8/h (Interquartile range (IQR), 4.5/h–10.8/h), with a median mean duration of 12.3 s (IQR 10.7–14.4 s). The mean duration of LMM was longer in NREM sleep (median 12.7 s, IQR 11.1–15.2 s) compared to REM sleep (median 10.4 s, IQR 8.3–13.4 s, $p < 0.001$). LMM with the longest mean durations were those associated with awakenings (median 18.0 s, IQR 16.0–21.0 s). Isolated LMM constituted 14.7% of the total LMM, with the majority of LMM occurring either with arousals or awakenings (83.3%). LMM indices in TST and NREM sleep were significantly higher in men compared to women ($p = 0.017$ and 0.029).

**Conclusions:** This is the first study to provide normative data on the prevalence of LMM in healthy adults. LMM are a ubiquitous phenomenon that often occurs in association with other events. While data are already available for children, in adults, the clinical significance of LMM in sleep disorders and in relation to sleep quality awaits further investigation.

**Disclosure**: No

### O184/P754 | Susceptibility changes in the brainstem reflect REM sleep without atonia severity in isolated REM sleep behavior disorder

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**Introduction:** REM sleep without atonia (RWA) is the neurophysiological hallmark of isolated REM sleep behavior disorder (iRBD) and is considered as one of the earliest signs of synucleinopathies, caused by neurodegeneration of brainstem structures involved in REM sleep regulation. Previously quantitative susceptibility mapping (QSM) method was proved to detect microstructural tissue changes in neurodegenerative diseases based on alteration of iron and myelin levels. The goal of the current study was to

(1) compare brainstem susceptibility in iRBD and controls using the voxel-based QSM approach and

(2) examine the association between brainstem susceptibility and the severity of RWA.

**Methods:** Sixty polysomnographically confirmed iRBD patients (age 67 ± 7 years) and 41 healthy controls (age 63 ± 10 years) were included in the study. RWA was quantified according to the SINBAR scoring method. QSM maps were reconstructed with QSMbox software from a multi-gradient-echo sequence acquired at 3 T MRI system and normalized using a custom-made T1 template. Voxel-based analysis with age as covariate was performed using two-sample *T*-test model for between-group comparison and using linear regression model for association with the SINBAR score. Statistical maps were generated using a cluster definition threshold of $p < 0.005$ and cluster-wise family-wise error (FWE) corrected threshold of $p < 0.05$.

**Results:** Compared to controls, the iRBD group had higher susceptibility in bilateral substantia nigra (SN) and nucleus ruber (NR), and periaqueductal grey. There was significant positive correlation between susceptibility values and SINBAR score in the left SN in iRBD patients ($p < 0.05$, FWE-corrected).

**Conclusions:** The voxel-based QSM analysis revealed abnormalities in several brainstem structures in iRBD. Increased susceptibility in SN was associated with the intensity of RWA suggesting increasing iron content related to RWA severity.

**Disclosure**: No

## O199/P755 | Effects of acute exposure to altitude on restless legs syndrome

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**Introduction:** Genetic factors, brain iron dysregulation and dopaminergic dysfunction play an important role in the pathogenesis of restless legs syndrome (RLS). Previous studies suggested also a role of hypoxia. Aim of this study was to investigate the effect of acute exposure to high-altitude on periodic leg movements during wakefulness (PLMW) and RLS symptoms during a suggested immobilization test (SIT) in RLS patients.

**Methods:** Twenty-eight RLS individuals underwent 1-h SIT twice in the same setting on two separate days: in randomized order, double-blinded, in a simulated high-altitude environment corresponding to 3000m above sea level, and at 574 m. PLMW were calculated. Subjective discomfort and urge to move the legs were assessed at baseline and every 15 min using a visual analogue scale 0–100.

**Results:** Twenty-eight RLS patients aged 45.1 ± 10.8 years were included, 53.6% female. PLMW index at 574 m was 26.5 ± 33.6, compared to 33.3 ± 48.6 at 3000 m ($p = 0.289$). Subjective discomfort and urge to move the legs both increased with time during SIT, and were worse at 3000 m (urge to move the legs at 30 min after SIT onset 16.4 ± 20 vs 24.5 ± 28.2, $p = 0.043$; at 45 min 21.4 ± 24.1 vs 29.4 ± 30.5, $p = 0.039$). When analysing both sex separately, the difference was still present only in males: I. subjective discomfort and urge to move were higher at 3000 m compared to 574 m 30 min after SIT onset (8.5 ± 16.8 vs 11.8 ± 19.3, $p = 0.045$, and 7.1 ± 12.5 vs 14.9 ± 19, $p = 0.006$); II. urge to move the legs was stronger at high altitude after 45 min from SIT onset (13.3 ± 22.6 vs 21.8 ± 25.6, $p = 0.019$); III. PLMW index during SIT was 20.8 ± 30.9 at 574 m vs 28 ± 37.1 at 3000 m, $p = 0.029$.

**Conclusions:** In patients with RLS, urge to move the legs is stronger at high-altitude. The effect of altitude was present only in male RLS patients, on both sensory and motor subjective symptoms, as well as PLMW index. These data support the role of peripheral hypoxia in RLS. Further studies assessing influence of RLS treatment, including a control group, as well as studies investigating pathophysiological mechanisms underlying the interaction between sex and hypoxia are needed.

**Disclosure**: No

## O201/P756 | Pervasive and diffuse muscle activity during rem and nrem sleep differentiates multiple system atrophy and Parkinson's disease

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**Objectives/Introduction:** Multiple system atrophy (MSA) and Parkinson's disease (PD) may share overlapping features particularly at early disease stage, including sleep alteration, but have profoundly different prognoses. Certain sleep phenomena and disorders of motor control are more prevalent in MSA, such as prominent motor dyscontrol during sleep and REM sleep behavior disorder (RBD). Tonic electromyographic (EMG) activity of submentalis and tibialis anterior muscles has been reported as common in subjects with MSA compared to those with obstructive sleep apneas, although without quantitative confirmation. We applied a novel automatic EMG analysis technique (DNE: PMID 28329117) to investigate whether pervasive muscle activity during non-REM sleep and REM sleep occurred in different muscles in subjects with MSA vs. PD.

**Methods:** Laboratory polysomnographic studies were performed in 50 consecutive subjects with PD and 26 age- and gender-matched subjects with MSA at < 5 years from disease onset. The DNE analysis focused on submentalis and on bilateral wrist extensor and tibialis anterior muscles in different wake-sleep states during the night.

**Results:** Subjects with MSA had significantly higher activity of submentalis, wrist extensor, and tibialis anterior muscles than subjects with PD during non-REM sleep, including separately in stages N1, N2, and N3, and during REM sleep, but not during nocturnal wakefulness. DNE indexes of EMG activity of wrist extensor and tibialis anterior muscles during non-REM sleep were significantly higher in subjects with MSA and RBD than in those with PD with RBD.

**Conclusions:** With respect to PD, MSA is characterized by a pervasive and diffuse muscle over activity that involves axial and limb muscles and occurs not only during REM sleep, but also during non-REM sleep and between patients with comorbid RBD. In perspective, targeted studies with test and validation cohorts are needed to test whether submentalis and/or limb muscle activity during non-REM sleep and REM sleep is a useful prognostic or diagnostic biomarker for MSA.

**Disclosure**: No

## O202/P748 | a meta-analysis of periodic leg movements during sleep associated with antidepressant treatment

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**Objectives/Introduction:** To perform a meta-analysis of the effect of various antidepressants on the periodic leg movements during sleep (PLMS) index (number of PLMS per h of sleep).

**Methods:** Studies explicitly reporting data concerning the evaluation of the effects of antidepressants on the PLMS index obtained by polysomnography (PSG) were reviewed and selected. A random effects

model meta-analysis was carried out for the PLMS index. The level of evidence was also assessed for each paper included in the meta-analysis.

**Results:** Eight studies were included in the final meta-analysis, five interventional and three observational. Most studies were characterized by a Level III evidence (non-randomized controlled trials, with the exception of two studies which could be classified as Level IV (case series, case-control, or historically controlled studies). Selective serotonin reuptake inhibitors (SSRIs) were used in five out of eight studies. The analysis of the assessments involving SSRIs or venlafaxine showed an overall large effect size (confidence interval 0.76, 1.81) and clearly much larger than that obtained with the studies using the other antidepressants. Heterogeneity, however, was significantly high.

**Conclusions:** This meta-analysis confirms the previous reports on the increase in PLMS often associated with the use of SSRIs (and venlafaxine); however, the absent or smaller effects of the other categories of antidepressants needs to be confirmed by more numerous and better controlled studies.

**Disclosure**: Yes

**Conflict of Interest statement:** Consultation for Jazz, not related with the content of this abstract.

## 19: SLEEP DISORDERS - HYPERSOMNIA

### O005/P159 | Data-driven phenotyping of central disorders of hypersomnolence with unsupervised clustering: toward more reliable diagnostic criteria

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**Objectives/Introduction:** Recent studies fueled doubts as to whether all currently defined central disorders of hypersomnolence are stable entities, especially narcolepsy type 2 and idiopathic hypersomnia. New reliable biomarkers are needed and the question arises whether current diagnostic criteria of hypersomnolence disorders should be reassessed. The main aim of this data-driven observational study on neurological sleep disorders was to see if data-driven algorithms would segregate narcolepsy type 1, and identify more reliable subgrouping of individuals without cataplexy.

**Methods:** We used the newly developed agglomerative hierarchical clustering package *Bowerbird*, an unsupervised machine learning algorithm, to identify distinct hypersomnolence clusters in the large-scale European Narcolepsy Network database with data of 1078 unmedicated adolescents and adults. We included 97 variables, covering all aspects of central hypersomnolence disorders such as symptoms, demographics, objective and subjective sleep measures, and laboratory biomarkers. The primary aim of the study was subgrouping of patients without cataplexy. Advanced analyses (resampling and clustering evaluation metrics) were performed to test for cluster reproducibility and distinctness.

**Results:** Seven clusters were identified, of which the first four clusters included predominantly individuals with cataplexy. Clusters 5 and 6 consisting of 157 and 158 patients respectively, were the most distinctly grouped clusters and had good cluster reproducibility. These two clusters were dominated by patients without cataplexy and, amongst other variables, significantly differed in presence of sleep drunkenness, subjective difficulty awakening and weekend-week sleep length difference. Clusters 1-4 mainly consisted of people with narcolepsy type 1, and patients formally diagnosed as narcolepsy type 2 and idiopathic hypersomnia were evenly mixed in clusters 5 and 6.

**Discussion:** In the largest study on central disorders of hypersomnolence to date, we identified distinct data-driven subgroups within the central disorders of hypersomnolence population. Our results confirm NT1 diagnosis with multiple subtypes, contest inclusion of sleep-onset rapid eye moment periods (SOREMPs) in diagnostic criteria for people without cataplexy, and provide promising new variables for reliable diagnostic categories. Data-driven classification will result in a more solid hypersomnolence classification system with less vulnerability to single, instable features.

**Disclosure**: No

### O012/P160 | Urinary catecholamines and cortisol in central disorders of hypersomnolence

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**Objectives/Introduction:** To assess whether urinary secretion of catecholamines and cortisol is associated with diagnosis category among patients with hypersomnolence (narcolepsy type 1 (NT1), type 2 (NT2), idiopathic hypersomnia (IH), and others), and to determine the clinical, biological, and neurophysiological variables associated with these biomarkers.

**Methods:** 265 consecutive drug-free subjects (61% women, 32 ± 15 y) evaluated for hypersomnolence in a French Reference Center for Narcolepsy and Rare Hypersomnias were recruited: 68 patients with NT1, 22 NT2, 63 IH, and 112 without central disorder of hypersomnolence. 24-h urine collection was performed in standardized conditions for all participants (7:00 p.m.–7:00 p.m.), during

polysomnography (PSG) and multiple sleep latency tests (MSLT) recording at the sleep laboratory. Catecholamines (epinephrine, norepinephrine, dopamine), two metabolites (normetanephrine, metanephrine) and cortisol levels were measured in all urine samples. Clinical characteristics, MSLT and PSG and parameters (especially sleep fragmentation markers, sleep and wake bouts) were assessed in all patients; and CSF orexin levels in a subgroup ($n = 107$).

**Results:** Catecholamines and metanephrine levels did not differ between the four diagnosis groups, but cortisol levels were lower ($p = 0.02$) and normetanephrine levels were higher ($p < 0.0001$) in NT1 compared to other groups, in crude and adjusted models. Epinephrine, normetanephrine, and metanephrine levels (but not norepinephrine, dopamine) were negatively correlated with sleep efficiency ($p = 0.002$) and total sleep time ($p = 0.02$), and positively with wake time after sleep onset, microarousals ($p = 0.04$), apnea-hypopnea index ($p = 0.01$), periodic legs movements (PLMs) ($p = 0.01$), and PLMs associated with microarousals ($p = 0.04$). Normetanephrine and metanephrine levels were also strongly correlated with markers of sleep fragmentation (sleep and wake bouts). Hypertension and autonomic dysfunction were associated with higher epinephrine levels. No association was found between any of these biomarkers, disrupted nocturnal sleep complaint, Epworth sleepiness scale scores, MSLT results nor CSF orexin levels.

**Conclusions:** We found several correlations between urinary secretion of catecholamines and their metabolites and markers of sleep fragmentation that suggest a complex deregulation of the sympathovagal system in patients with hypersomnolence. No association was found between urinary biomarkers and objective or self-reported sleepiness. Lower 24-h secretion of urinary cortisol was shown in NT1 compared to other groups, which may relate to underlying low orexin levels.

**Disclosure**: No

## O014/P161 | Circadian variation of muscle atonia index in different levels of vigilance as a possible marker of narcolepsy compared to other hypersomnias: an MSLT based retrospective study

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**Objectives:** The diagnosis of narcolepsy is often complex and delayed, requiring extensive diagnostic tests and invasive procedures such as CSF orexin dosage. The complexity of the procedures and the complex clinical picture may induce substantial diagnostic delays. Our study aimed to evaluate circadian changes in muscle tone (atonia index) in different levels of vigilance during the multiple sleep latency test in patients with narcolepsy type 1 (NT1) and 2 (NT2) compared with other hypersomnias and evaluate its possible diagnostic value.

**Methods:** Twenty-nine patients with narcolepsy type 1 (11 M 18 F, mean age 34.9 years, SD 16.8) and sixteen with narcolepsy type 2 (10 M 6 F, mean age 34.9 years, SD 16.8) and 27 controls with other hypersomnias (14 M, 13 F mean age 45.1 years, SD 15.1). An evaluation of the muscle atonia index (AI) was carried out in different levels of vigilance (wake and REM sleep) in each nap and the entire MSLT of each group. The validity of AI in the identification of patients with narcolepsy (NT1 and NT2) was evaluated using Receiver Operating Characteristic (ROC) curves.

**Results:** AI during wakefulness (WAI) was significantly higher in both the narcolepsy groups (NT1 and NT2 $p < 0.001$) compared with the control hypersomniac group. AI during REM sleep (RAI) was lower in NT1 than NT2 ($p = 0.03$). The analysis of the ROC curves returned high AUC values for WAI (NT1 0.88; Youden index > 0.57 Sensitivity 79.3% Specificity 90%; NT2 0.89 Youden index > 0.67 Sensitivity 87.5% Specificity 95%; NT1 and NT2 0.88 Youden index > 0.57 Sensitivity 82.2% Specificity 90%) in discriminating subjects suffering from different central hypersomnias. RAI showed an AUC value of 0.7 (Youden index ≤0.7 Sensitivity 50% Specificity 87.5%), differentiating NT1 and NT2.

**Conclusions:** AI during wakefulness seems to be a promising electrophysiological marker of narcolepsy and suggests a vulnerable tendency to dissociative waking/sleep dysregulation absent in other forms of hypersomnia.

**Disclosure**: No

## O015/P162 | Hypocretin-1 measurements in cerebrospinal fluid using radioimmunoassay: within and between assay reliability and limit of quantification

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**Objectives/Introduction:** The most sensitive and specific investigative method for the diagnosis of narcolepsy type 1 (NT1) is the determination of hypocretin-1 (orexin A) deficiency (≤110 pg/ml) in cerebrospinal fluid using a radioimmunoassay (RIA). We aimed to assess the reliability of the Phoenix Pharmaceuticals hypocretin-1 RIA, by determining the lower limit of quantification (LLOQ), the variability around the cut-off of 110 pg/mL and the inter- and intra-assay variability.

**Methods:** Raw data of 80 consecutive hypocretin-1 RIAs were used to estimate the intra- and inter-assay coefficient of variation (CV). The LLOQ was established, defined as the lowest converted concentration with a CV < 25%; the conversion is performed using a harmonization sample which is internationally used to minimize variation between RIAs.

**Results:** The mean intra-assay CV was 4.7%, while the unconverted inter-assay CV was 28.3% (18.5% excluding 2 outliers) and 7.5% when

converted to international values. The LLOQ was determined as 27.9 pg/ml. The intra-assay CV of RIAs with lower specific radioactive activity showed a median of 5.6% ($n = 41$, range 1.6%–17.0%), which was significantly higher than in RIAs with higher specific activity ($n = 36$; median 3.2%, range 0.4%–11.6%, $p = 0.013$). The CV around the 110 pg/ml cut-off was < 7%.

**Conclusions:** Hypocretin-1 RIAs should always be harmonized using standard reference material. The specific activity of an RIA has a significant impact on its reliability, because of the decay of $^{125}$I radioactivity. Values around the hypocretin-1 cutt-off can reliably be measured. Hypocretin-1 concentrations below 28 pg/ml should be reported as "undetectable" when measured with the Phoenix Pharmaceuticals RIA.

**Disclosure**: No

## O083/P474 | Efficacy and safety of pitolisant in children above 6 years with narcolepsy with and without cataplexy

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**Objective:** Narcolepsy is a rare neurological disorder frequently occurring from childhood and persisting through adulthood. Pitolisant, a selective histamine H3-receptor antagonist/inverse agonist, obtained an EMA/FDA approval for the treatment of Excessive Daytime Sleepiness (EDS) and cataplexy in adult narcolepsy patients. We assessed the pitolisant efficacy and safety on EDS and cataplexy in children 6–17 years old with narcolepsy with or without cataplexy.

**Methods:** This is a double-blind, multicenter, randomized, placebo-controlled study including children with narcolepsy (ICSD-3) with a Pediatric Daytime Sleepiness Scale (PDSS) score ≥15 who were randomly assigned to pitolisant or placebo (2:1) once-a-day for 4-week flexible dosing (5–40 mg pitolisant) followed by 4-week stable dosing. The primary endpoint was the EDS and the cataplexy improvement as measured by the Ullanlinna Narcolepsy Scale (UNS). The UNS is an 11-item scale used to measure intensity and frequency of symptoms of narcolepsy. 4 items address cataplexy and 7 items measure the propensity to fall asleep in various situations. Score varies from 0 to 44. Main secondary endpoints were changes in PDSS, UNS catapexy subscore (UNSctp), cataplexy episodes per week (WRC), maintenance of wakefulness test (MWT) and safety.

**Results:** Among 115 selected patients, 110 were randomised, 72 to pitolisant and 38 to placebo. The UNS score reduced from 24.63(7.8) to 18.23(8.14) in Pitolisant and from 23.68(9.08) to 21.77(9.25) in placebo group: the efficacy of Pitolisant was significantly higher than placebo (difference:−3.69 (1.37), $p = 0.0073$). PDSS reduced from 20.16 (3.64) to 14.57(5.37) with Pitolisant vs 20.00(3.49) to 17.96(5.6) with placebo ($p = 0.0015$). The UNSctp also decreased with Pitolisant (−2.88) vs pl (−1.12) ($p = 0.029$). The reduction of WRC was higher in Pitolisant from 8.63 to 5.39 versus 13.44 to 10.73 with placebo ($P = 0.32$) but not significantly different. The MWT was significantly increased in Pitolisant from 10.14 min to 11.47 min versus placebo 10.61–10.19 (Hazard Ratio HR 0.748 [0.616, 0.903], $p = 0.004$). The most frequent adverse events for Pitolisant were headache (19.2%; 8.1% for placebo) and insomnia (6.8%; 2.7% for placebo).

**Conclusion:** In Narcolepsy children above 6 years old, Pitolisant 5–40 mg/day demonstrates significant efficacy in reducing Excessive Daytime Sleepiness and cataplexy and is well tolerated.

**Disclosure**: Yes

**Conflict of Interest statement:** The study was sponsored by bioprojet. Giuseppe Plazzi, Michel Lecendreux, Gert Jan Lammers, Patricia Franco, Mikhail Poluektov, Yves Dauvilliers were investigators. Martine Le Gall, Isabelle Lecomte are bioprojet employees

Jeanne-Marie Lecomte and Jean-Charles Schwartz are founders of bioprojet

## O087/P475 | Idling for decades: a european study on risk factors associated with the delay before a narcolepsy diagnosis

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**Objectives/Introduction:** Narcolepsy type-1 (NT1) is a rare chronic neurological sleep disorder with excessive daytime sleepiness (EDS) as usual first and cataplexy as pathognomonic symptoms. Shortening the NT1 diagnostic delay is the key to reduce disease burden and related low quality of life. Here we investigated the changes of diagnostic delay over the diagnostic years (1990–2018) and the factors associated with the delay in Europe.

**Methods:** We analyzed 580 NT1 patients from 12 European countries using the European Narcolepsy Network database. The diagnostic delays between patients diagnosed in different years and in different countries were compared using Kruskal-Wallis rank sum test. Post-hoc pairwise comparisons were done using Conover's test with *p*-values adjusted by Benjamini & Hochberg method. We then combined machine learning and linear mixed-effect model (LMM) to identify factors associated with the delay.

**Results:** The mean age of EDS onset and diagnosis of our patients was 20.9 ± 11.8 (mean ± standard deviation) and 30.5 ± 14.9 years old, respectively. Their mean and median diagnostic delay was 9.7 ± 11.5 and 5.3 (interquartile range: 1.7 –13.2 years) years, respectively. We did not find significant differences in the diagnostic delay over years in the whole dataset (P-value = 0.263), although the delay showed significant country differences (*p*-value < 0.0001). The number of patients with short (≤2-year) and long (≥13-year) diagnostic delay equally increased over decades, suggesting that subgroups of NT1 patients with variable disease progression may co-exist. Younger age of cataplexy onset, longer interval between EDS and cataplexy onsets, lower cataplexy frequency, shorter duration of irresistible daytime sleep, lower daytime REM sleep propensity and females are associated with longer diagnostic delay.

**Conclusions:** Our findings contrast the results of previous studies reporting shorter delay over time which is confounded by calendar year, because they characterized the changes in diagnostic delay over the symptom onset year. New strategies such as increasing media attention/awareness and developing new biomarkers are needed that better detect EDS, cataplexy and changes of nocturnal sleep in narcolepsy, in order to shorten the diagnostic interval.

**Disclosure**: No

## O181/P763 | Ambulatory circadian monitoring differences between narcolepsy type 1 and idiopathic hypersomnia

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**Introduction:** The diagnosis in the spectrum of Central Hypersomnias (CH) is sometimes difficult in borderland cases. Nocturnal sleep is usually more fragmented in Narcolepsy type 1 (NT1) than in Idiopathic Hypersomnia (IH). Typical NT1 patients show frequents awakenings and arousals, while IH have longer and less interrupted sleep. On the other hand, it has been reported that temperature regulation is impaired in NT1 patients, reflecting both the daytime sleepiness and nocturnal sleep fragmentation, however there are limited data comparing the differences with other CH.

**Methods:** We monitored distal skin (wrist) temperature (WT), activity, body position, environmental light and temperature rhythms of 5 long sleep IH patients (35.4 ± 5.4 years old, 80% women) and 10 NT1 patients without medication (40.3 ± 3.3 years old, 50% women) for one week under free-living conditions. Circadian patterns were characterized using a non-parametrical analysis to assess differences between groups. Values of $p < 0.05$ were considered to be statistically significant.

**Results:** WT pattern of IH compared to NT1 patients exhibited higher stability (0.53 ± 0.05 vs 0.48 ± 0.04, $p < 0.05$) robustness (0.50 ± 0.02 vs 0.44 ± 0.02, $p < 0.05$) and nocturnal values (35.39 ± 0.36°C vs 34.46 ± 0.17°C, $p < 0.01$) and a lower fragmentation (0.15 ± 0.02 vs 0.22 ± 0.02, $p < 0.05$). IH patients showed a less fragmented (0.52 ± 0.01 vs 0.80 ± 0.09, $p < 0.05$), and an advanced nocturnal phase (03:38 ± 00:39 vs 04:59 ± 00:20, $p < 0.05$) than NT1 patients for the activity pattern. Regarding body position pattern, IH patients showed higher stability (0.62 ± 0.05 vs 0.51 ± 0.03, $p < 0.05$) and daytime values (52.23 ± 1.46°vs 45.85 ± 1.66°, $p < 0.05$) than narcoleptic patients. IH patients exposed themselves to higher environmental temperatures than narcoleptic patients during nighttime (24.59 ± 1.98°C vs 20.97 ± 0.46°C, $p < 0.05$) and daytime (28.89 ± 1.45°C vs 25.86 ± 0.46°C, $p < 0.01$).

**Conclusions:** The results of a full week circadian ambulatory recording support the concept that nocturnal sleep is more stable in IH than in NT1. Nocturnal WT is higher in IH than in NT1, and sleep is less fragmented in patients with IH than in NT1. These data suggest than some circadian parameters might help to differentiate a narcoleptic circadian profile from an IH profile based on data from routine patients' life

**Disclosure**: No

## O185/P764 | Pupillometry biomarkers to differentiate idiopathic hypersomnia from narcolepsy type 1

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**Objectives/Introduction:** Hypersomnia spectrum disorders remain underdiagnosed and insufficiently treated in the absence of biomarkers. Light is known to exert strong alerting effects on human behavior thanks to melanopsin-based photo transduction, a retinal photo pigment sensitive to blue light. Photo transduction index obtained from specific pupillometry tool have been recently identified as biomarkers of disorders. In this context to identify biomarkers of hypersomnia subtypes, we investigated the melanopsin pupil response (Post-Illumination Pupil Response, PIPR) and the variation of the pupil diameter in patients with idiopathic hypersomnia (IH) with prolonged total sleep time (TST > 660 min), as well as in patients with narcolepsy type 1 (N1) and healthy subjects.

**Methods:** Pupil diameter's variations were measured during 25 min with an infrared pupillometry setup alternating prolonged periods of darkness and light exposure as follows: darkness/red light/darkness/blue light/darkness. The PIPR was recorded after exposure to blue light and calculated as relative to the baseline pupil diameter (relative PIPR%). Multiple logistic regression (with group as dependent factor) coefficients adjusted on age and sex were calculated to compare the pupil diameter and the relative PIPR between groups.

**Results:** Twenty-seven patients with N1 (women 59%, 36 y ± 1.8), 36 patients with IH (women 83%, 27.2 y ± 1.2) and 43 healthy subjects (women 58%, 30.6 y ± 1.4) were included. Patients with N1 and IH obtained a lower relative PIPR (respectively 31.6 ± 2.7% and 33.2 ± 1.7%) as compared to controls (38.7 ± 1.5%) suggesting a reduced melanopsin response in both hypersomnia subtypes ($p < 0.05$). However, patients with N1 obtained a reduced baseline pupil diameter compared to controls (4.4 ± 0.2 *vs* 5.2 ± 0.2 mm, $p = 0.03$) and a reduced pupil diameter after blue light compared to IH (2.86 ± 0.1 *vs* 3.5 ± 0.1 mm, $p = 0.02$).

**Conclusions:** This study reports that IH and N1 were both associated with an alteration of the melanopsin-based photo transduction and N1 with a reduced pupil diameter. Thus, the PIPR and the pupil size may be promising combined markers to distinguish IH from N1.

**Disclosure**: No

## O203/P765 | Telemonitoring with fitbit inspire 2 in central disorders of hypersomnolence

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**Introduction:** The multicentre Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (SPHYNCS) aims to identify new biomarkers for narcolepsy and its borderland (NBL). Although narcolepsy type 1 (NT1) is well characterized, NBL disorders such as idiopathic hypersomnia (IH) and other central hypersomnias (OCH) lack precise diagnostic biomarkers. Ambulatory monitoring in clinical routine is limited to actigraphy over 1-2 weeks. Fitbit devices have been shown to monitor sleep, physical activity and physiological parameters over several consecutive months. This study aims to identify new digital biomarkers of narcolepsy and NBL using a Fitbit device.

**Methods:** Between January 2020 and March 2022, 77 patients with central disorders of hypersomnolence and 12 healthy controls (HC) were included in the ongoing SPHYNCS study, and 71 participants agreed to wear a Fitbit device. Compliance, defined as the percentage of weeks the device was used at least six days per week, was calculated for each subject. Daily resolution Fitbit features and minute resolution activity and heart rate data were analysed for the two weeks each participant wore the device most consistently, that is, for the two weeks with less missing data. Fifty subjects were included in the two-week analysis.

**Results:** 71 participants (54 females, 17 males) with an average age of 28 years (range 17–56) received the Fitbit. The overall compliance of 75% (82% for HC, 55% for NT1, 66% for IH, and 71% for OCH) for a total of 42 years of Fitbit data. In the preliminary two-week analysis, Fitbit features like time in bed and number of steps were not significantly different between the four participant groups. However, the maximum and average heart rate differed between groups ($p$-value of 0.02 and 0.05, respectively, Kruskal-Wallis H-test). On average, HC showed the highest maximum heart rate, and the NT1 showed the lowest heart rate minimum.

**Conclusion:** Preliminary results of this ongoing study suggest that Fitbit monitoring for an extended period, with a focus on minute resolution activity and heart rate data, has the potential to identify novel biomarkers for NT1 and its borderland.

**Disclosure**: No

## O204/P766 | Executive function and fatigue in pediatric narcolepsy type 1

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**Introduction**: Executive functions - higher order cognitive functions involved in execution of goal directed behavior - is important for daily life activities and academic performance. High rates of executive dysfunctions (EDF) have been reported from both adult and pediatric narcolepsy populations. Fatigue, also a common complaint in adult and pediatric narcolepsy patients, mainly refers to a subjective experience of mental or physical exhaustion that does not disappear after a period of sleep. To our knowledge it is unknown whether fatigue and EDF are associated in pediatric narcolepsy. Findings from other neurological disorders suggest that fatigue is associated with cognitive

dysfunction when assessed by questionnaires in contrast to associations with performance on neuropsychological tests. The aim of the present study was to assess the association between EDF measured by a parent reported questionnaire and self - reported fatigue in pediatric narcolepsy type 1.

**Methods**: After written informed consent, we consecutively included 50 youths aged 7–20 (mean (SD) age 14.8 (3.3), 28/56 females, 44/50 Pandemrix (H1N1)-vaccinated, 49/50 hypocretin-1 - deficient) with narcolepsy type 1(NT1) admitted to our national center of expertise for narcolepsy in Norway. All patients fulfilled ICSD-3 criteria for NT1. EDF were measured by parent report of behavior on the Behavior Rating Inventory of Executive Function (BRIEF, higher scores indicate poorer function), while fatigue was measured by the Pediatric quality of life multidimensional

self - report fatigue scale (lower scores indicate poorer function).

**Results:** 32/50 had a BRIEF score in a clinically relevant level, most frequently working memory difficulties (24/50). Mean total fatigue score was poor (48.4), more severe than those reported for several other chronic medical disorders; poorest score (39.0) was on the sleep/rest fatigue subscale. Total fatigue score was significantly correlated with BRIEF global score ($rho = -0.524$, $p < 0.000$).

**Conclusions:** EDF and fatigue were highly prevalent, and significantly and moderately correlated in our pediatric NT1 cohort. Whether fatigue leads to impaired cognitive function or EDF lead to exertion and fatigue may not be derived from this cross sectional study, and whether a common disease related factor leads to both fatigue and EDF needs to be investigated further.

**Disclosure**: Yes

**Conflict of Interest statement:** Stine Knudsen-Heier has been an expert consultant for the Norwegian state.

O206/P767 | **Solriamfetol real world experience study: initiation, titration, safety, effectiveness, and experience during follow-up for patients with narcolepsy from Germany**

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**Objectives/Introduction:** Excessive daytime sleepiness (EDS) is a symptom of narcolepsy that may be managed with wake-promoting agents or sodium oxybate. Solriamfetol (Sunosi™) is a dopamine/norepinephrine reuptake inhibitor approved to treat EDS associated with narcolepsy (75–150 mg/day). This real-world study characterises dosing/titration strategies among European physicians initiating solriamfetol and patient outcomes following initiation.

**Methods:** This is an ongoing retrospective chart review conducted by physicians in Germany, France, and Italy. Data are reported from 70 German patients with narcolepsy. Eligible patients (≥18 years old, diagnosed with EDS due to narcolepsy, had reached a stable solriamfetol dose, and had completed ≥6 weeks of treatment) were classified into 1 of 3 groups based on solriamfetol initiation strategy: changeover (switched/switching from existing EDS medication[s]), add-on (added/adding to current EDS medication[s]), or new-to-therapy (no current/previous EDS medication).

**Results:** Patients' mean ± SD age was 36.9 ± 13.9 years; 56% were female and 57% experienced cataplexy. Anxiety/depression was the most frequently reported comorbidity (36%). Changeover was the most common initiation strategy ($n = 43$), followed by add-on ($n = 19$), then new-to-therapy ($n = 8$). The most common starting doses of solriamfetol were 75 ($n = 48$; 69%) and 150 mg/day ($n = 14$; 20%). Solriamfetol was titrated in 29 patients (41%); most were titrated within 7 days. Mean ± SD Epworth Sleepiness Scale (ESS) score was 17.6 ± 3.1 ($n = 61$) at initiation and 13.6 ± 3.8 at follow-up ($n = 51$), with a mean decrease of 4.3 ± 2.9 points. Across subgroups, mean ESS scores at initiation and follow-up ranged from 17.1–18.5 and 11.5–15.0, respectively, with mean decreases from 3.7–6.1 points. Slight to strong improvements in EDS after solriamfetol initiation were reported for most patients (patient report, 91%; physician report, 94%). Most patients (72%) reported no change in their perceived night-time sleep quality. Common adverse effects were headache, decreased appetite, and insomnia. No cardiovascular events were reported.

**Conclusions:** These real-world data describe the use of solriamfetol in a cohort of German patients with narcolepsy. Solriamfetol was typically initiated at 75 mg/day; titration was common. ESS scores improved across all subgroups; most patients and physicians perceived improvement in EDS. Common adverse events were consistent with those previously reported for solriamfetol.

**Disclosure**: Yes

**Conflict of Interest statement: Funding statement:** This study was funded by Jazz Pharmaceuticals.

**Conflicts of Interest**: Y Winter has received honoraria for educational presentations and consultations from Arvelle Therapeutics, Angelini Pharma, Bayer AG, BIAL, Bioprojet Pharma, Bristol Myers Squibb, Eisai, Ethypharm GmbH, GW Pharmaceuticals, Jazz Pharmaceuticals, LivaNova, Neuraxpharm, Novartis, and UCB Pharma not related to the current study.

**G Mayer** is on the advisory board for Janssen Pharma in Germany and NLS Pharma in Basel, Switzerland.

**S Kotterba, H Benes,** and **L Burghaus** have nothing to disclose.

**A Koch, D Girfoglio,** and **M Setanoians** are employees of Jazz pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

**U Kallweit** is on the advisory board at AOP Orphan Pharmaceuticals, Bioprojet Pharma, Jazz Pharmaceuticals, Harmony Biosciences,

Takeda Pharma, and UCB Pharma. He is also a consultant to AOP Orphan Pharmaceuticals, Bioprojet Pharma, Jazz Pharmaceuticals, Harmony Biosciences, and Takeda Pharma, and has accepted grants/research support from Bioprojet Pharma, Jazz Pharmaceuticals, and Harmony Biosciences.

## 20: NEUROLOGICAL DISORDERS AND SLEEP

### O038/P178 | objective long sleep and inflammation levels predict cognitive decline among non-demented elderly: preliminary findings from the Cretan Aging Cohort.

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**Objectives/introduction:** Sleep disturbances and inflammation have been linked with cognitive decline and previous cross-sectional studies have shown that long sleep duration and increased inflammatory markers associate with disease severity in patients Mild Cognitive Impairment (MCI) and Dementia.

We examined the longitudinal associations between objective sleep, inflammatory markers and cognitive progression in non-demented community-dwelling elderly.

**Methods:** A sub-sample of 89 participants (75.3% females) from a large population-based cohort in Crete, Greece of older adults (>60 y) (Phase II) were followed-up 8 years later (phase III). All participants underwent neuropsychiatric/neuropsychological evaluation (phases II & III) and a 3-day 24 h actigraphy and pro-inflammatory cytokines IL-6 and TNFα plasma levels (phase II).

Participants were diagnosed as CNI ($N = 48$) and MCI ($N = 41$) during phase II, whereas during phase III 28 were diagnosed with CNI, 40 with MCI and 21 with Dementia. On follow-up, 41(46%) participants deteriorated to a cognitively worse diagnosis compared to phase II, while 48 did not. Objective sleep variables and inflammatory markers at phase II were compared between the deteriorated vs. the non-deteriorated groups using ANCOVA. Also, differences in neuropsychological testing scores (phase II- phase III) were calculated and their associations with sleep variables were examined using partial correlation models.

**Results:** The deteriorated group compared to non-deteriorated had significantly longer night total sleep time (TST) (424 ± 57.2 min vs. 400 ± 75.7 min, $p = 0.043$), night total time in bed (TMB) (518 ± 62.8 min vs. 490 ± 86.2 min, $p = 0.039$), and marginally longer24-h TST (459 ± 85min vs. 433 ± 79 min, $p = 0.064$), 24-h TMB (572 ± 98 min vs. 539 ± 95 min, $p = 0.057$), as well as higher TNFα levels (1.23 ± 0.09 pgr/ml vs. 1.01 ± 0.09 pgr/ml, $p = 0.07$). IL-6 levels did not differ between the two groups. Worsening in immediate memory recall correlated with 24-h TMB ($r = 0.269$) and wake time after sleep onset ($r = 0.286$). Finally, night sleep efficiency associated with decline in verbal and episodic short-memory recall indices (−0.230 and −0.256, respectively).

**Conclusions:** These preliminary results indicate that almost half of the participants deteriorated cognitively in 8 years. Long sleep and higher TNFα levels at baseline predict deterioration of clinical cognitive status at follow-up and may be novel and clinically useful prognostic biomarkers of cognitive decline.

**Disclosure**: Yes

**Conflict of Interest statement:** National Strategic Reference Framework (NSRF) - Research Funding Program: THALES entitled "UOC-Multidisciplinary network for the study of Alzheimer's Disease" Grant Cod: MIS 377299

HELLENIC FOUNDATION FOR REASEARCH AND INNOVATION (HFRI)- Research Funding Program: ELIDEK entitled "Sleep Apnea (OSA) and poor sleep as Risk Factors for decreased cognitive performance in patients with Mild Cognitive Impairment: the Cretan Aging Cohort (CAC)", Grant Cod: *HFR1-FM17-4397*

### O084/P491 | The effects of sleep on seizure dynamics in drug-resistant focal epilepsy

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**Objectives:** There is a tight link between sleep and epilepsy. Sleep has been shown to have important influences on focal interictal epileptiform discharges (IEDs), with the rates and spatial extent of IEDs increased in non-rapid eye movement (NREM) sleep. Conversely, the influence of sleep on seizures is less clear and, in particular, its effects on seizure topography are poorly documented. Here, we assessed how NREM sleep affects the spatiotemporal dynamics of seizures.

**Methods:** Fifteen patients with drug-resistant focal epilepsy (9 females; mean age: 34.1 ± 7.7 years; 6 temporal lobe epilepsy) who underwent stereo-electroencephalography (SEEG) with intracerebral electrodes for presurgical investigation were included. In each patient, we selected the first 1-3 seizures that occurred during wakefulness and NREM (N2/N3) sleep, within a 48-h time window and under the same antiepileptic drug regimen. Seizures were marked manually in the bipolar montage. 10-min epochs of the interictal SEEG were selected during wakefulness and NREM (N2/N3) sleep, and IEDs were detected automatically to compare the effects of sleep on IEDs and seizures.

**Results:** There were no significant differences between wakefulness and NREM in the spatial distribution of the seizure onset, seizure onset pattern, latency to maximal channel involvement during the seizure, spatial propagation of the seizure, the appearance and latency of ictal high-frequency activity as measured by the epileptogenicity index, or total seizure duration (all $p > 0.05$). Similarly, the number of propagation clusters, defined as groups of channels that become involved in the seizure together within a 500-ms window, and the

mean time interval between propagation clusters were not significantly different between the vigilance states ($p > 0.05$). In contrast, as expected, the rates and spatial distribution of IEDs were increased in NREM sleep compared to wakefulness (both $p = 0.0002$, Cliff's $d = 0.37$ and 0.51). The spatial overlap between wakefulness and NREM sleep was higher in seizures (67.7 ± 31.2%) compared to IEDs (36.4 ± 36.3%) ($p = 0.002$, Cliff's$d = 0.72$).

**Conclusions:** In contrast to its effects on IEDs, NREM sleep does not affect the spatiotemporal dynamics of seizures. Therefore, our results suggest that once the brain surpasses the threshold for generating a seizure, it will follow the underlying network irrespective of the vigilance state.

**Disclosure**: Yes

**Conflict of Interest statement:** Disclosures outside of the submitted work: Birgit Frauscher has had advisory board meetings and speaking engagements from UCB and Eisai as well as industrial funding from Eisai in the last year. All other co-authors have no conflicts of interest to declare.

This work is supported by the Canadian Institutes of Health Research, the Fonds de Recherche du Québec – Santé, the Hewitt Foundation, and the Montreal Neurological Institute.

## O183/P783 | Melanopsin-mediated pupil response is associated with executive functioning in alpha-synucleinopathies

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**Objectives/Introduction:** α-synucleinopathies are clinically characterized by parkinsonism and dementia, with isolated REM sleep behavior disorder (iRBD) representing a prodromal phase. Neurodegenerative processes are reflected in the retina. In Parkinson´s disease, retinal impairment is restricted to dopaminergic retinal layers such as the retinal ganglion cells (GCs). Chromatic pupillometry can be used to assess functioning of melanopsin-expressing GCs. The aim of this study was to analyze the link between functioning of melanopsin-expressing GCs and cognition in patients with iRBD.

**Methods:** We compared dark adapted chromatic pupil responses after a short blue light stimulus (1 sec) with cognitive functioning (CERAD-Plus) of 69 patients with iRBD. Of these patients, 10 were diagnosed with mild neurocognitive disorder. For cognition, two composite scores for executive functioning and global cognition were formed. Patients were staged based on dopamine-transporter density (DaT-SPECT). A *z*-score of > 2.0 standard deviation below reference in the right or left posterior putamen was defined as advanced state. We used post-illumination pupil response (PIPR) after 6 sec as a marker of melanopsin activity and minimal pupil size (MPS) as a marker of rods and cones activity.

**Results:** Patients with mild neurocognitive disorder demonstrated a reduced PIPR-amplitude (indicating an impaired function of melanopsin) compared to patients without ($p = 0.001$). Global cognition demonstrated a weak significant association with PIPR ($r = 0.292$, $p = 0.015$). Executive functioning demonstrated a medium significant association with PIPR ($r = 0.417$, $p < 0.001$), and a strong association in patients with advance state based on DaT-SPECT-density ($r = 0.575$, $p = 0.002$). MPS was not significantly associated with cognition ($p > 0.05$).

**Conclusions:** Results suggest an association between executive dysfunction and melanopsin dysfunction assessed by a reduced PIPR-amplitude in prodromal α-synucleinopathies. Based on the low-cost, easy-to-use profile, chromatic pupillometry might be a non-invasive biomarker of executive functioning in α-synucleinopathies widely applicable for clinical context.

**Disclosure**: No

## O186/P784 | A 10 year study of sleep in huntington's disease: Abnormal sleep period activity is associated with cognitive decline

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**Introduction:** Sleep and circadian abnormalities form a significant aspect of many neurodegenerative conditions. They are a focus of current research due to their potential to exacerbate symptomatology and disease progression. Huntington's disease (HD) provides a unique insight into this question, because as a monogenic fully penetrant neurodegenerative condition, it facilitates longitudinal study of sleep abnormalities versus clinical outcomes from the presymptomatic period. Here we present results from the first such study in a clinical cohort.

**Methods:** 28 premanifest HD gene carriers (9 male, age 44 ± 11.4) and 22 controls (10 male, age 45 ± 16.2) underwent clinical motor, psychiatric and cognitive assessments and 14-day actigraphy at two time points, 10 years apart (9.8 ± 1.0 years). Parameters of wake and sleep period onset time and activity levels, plus measures of circadian interdaily stability and intradaily variability, were derived from actigraphs. Data was analysed (i) cross-sectionally at baseline and follow up, and (ii) longitudinally using a repeated measures general linear model, controlling for age and sex. Multivariate regression analyses were used to explore associations between actigraphy and clinical outcomes.

**Results:** 20 HD gene carriers and 15 controls underwent follow up assessment. 7 HD gene carriers phenoconverted to manifest disease. At baseline, there were no differences between groups on any clinical or actigraphy variable. At follow up, manifest gene carriers exhibited expected deficits in psychomotor speed (Symbol Digit Modalities Task [SDMT], $p = 0.008$), executive function (Trail B Task [TrB], $p = 0.003$) and learning/memory (delayed Hopkins verbal learning task [dHVLT], $p = 0.005$). Manifest gene carriers also exhibited significantly higher

sleep period activity levels than premanifest gene carriers and controls, evident in both cross-sectional ($p = 0.005$, $\eta^2 = 0.302$) and longitudinal models ($F = 3.70$, $p = 0.039$, $\eta^2_p = 0.228$). This was not evident in wake period activity levels, suggesting this activity was distinct from chorea. Sleep period activity was specifically and highly correlated with the cognitive dysfunction in gene carriers (SDMT $p = 0.002$, $R^2 = 0.533$; TrB $p = 0.004$, $R^2 = 0.494$; dHVLT $p = 0.007$, $R^2 = 0.455$).

**Conclusions:** These findings are consistent with a model in which abnormal sleep period activity is linked to cognitive decline in HD. Our ongoing polysomnographic and intervention studies are awaited to define this sleep period activity and interrogate causation from this association.

**Disclosure**: No

## O198/P785 | Beneficial or disruptive? Exploring gamma dynamics with direct recordings in human brainstem arousal circuits

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**Objectives:** Neurodegeneration of brainstem arousal circuits results in debilitating sleep and circadian rhythm disturbances. We examined the activity of human pedunculopontine nucleus (PPN) in relation to slow-wave sleep and quiet wakefulness to uncover physiology and pathological patterns.

**Methods:** Local field potentials (LFP) and combined polysomnography were recorded from four male patients with deep brain leads in the PPN for treatment of multiple systems atrophy, at least 72-h post-implantation. Sleep fragmentation was assessed per patient, based on number of continuous (>10 mins) sleep episodes and the number of awakenings. To examine relation to slow wave phase, we analysed PPN activity with 5-s snippets of associated continuous cortical slow oscillation trains. We also assessed connectivity between brainstem and cortex using the imaginary part of coherence and the non-parametric estimate of Grangers causality to assess directionality of information flow (multivariate autoregressive modelling, in-house Matlab scripts). Statistical analyses included a non-parametric cluster-based permutation procedure (controlling for multiple comparisons) and analysis of variance with sleep fragmentation index and clinical severity scores as additional factors.

**Results:** Wakefulness was associated with higher power in the beta (12–30 Hz) and gamma (30–80 Hz) range of the recorded LFPs from both hemispheres. Maximum modulation across states was observed for beta and high gamma (55–80 Hz) power, with significantly increased gamma coherence between cortex and brainstem occurring during wakefulness. Phase-amplitude coupling revealed that brainstem gamma activity is stronger during the UP-state of the cortical slow oscillation.

No statistically significant difference in bottom-up information flow was observed between cases during wakefulness. However, Grangers causality values for gamma increased significantly during sleep; this relationship persisted both within and across all patients and significantly correlated with poor sleep continuity.

**Conclusions:** Human PPN activity is characterized by beta and gamma oscillations during wakefulness, with bursts of gamma activity during the UP-state of the slow oscillation during sleep. In this cohort, increased bottom-up information flow is observed for wake-related frequencies during slow-wave activity. This could signify hyper activation of wake-promoting areas secondary to neurodegenerative changes. These findings provide direct evidence of the significance of gamma activity as a therapeutic target in conditions affecting brainstem arousal circuits.

**Disclosure**: No

## O200/P786 | Patients with drug-resistant epilepsy exhibit an impaired autonomic cardiac arousal response following sleep apnea

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**Objectives/Introduction:** Most sudden and unexpected deaths in epilepsy (SUDEP) are triggered by a generalised convulsive seizure occurring during sleep and might primarily result from post-ictal respiratory dysfunction. Whether or not patients with epilepsy might develop impaired apnea-related arousing response is unknown. To address this issue, we compared arousal responses to respiratory events in patients with drug-resistant epilepsy (DRE), patients with drug-sensitive epilepsy (DSE), and control subjects.

**Methods:** Sixty patients with obstructive sleep apnea (OSA) were retrospectively included: 20 controls, 20 DRE, and 20 DSE. The 3 groups were matched for age, sex, BMI and apnea-hypopnea index (AHI). The following parameters aiming to explore the physiological response to airflow reduction were determined on the polysomnography: the cortical arousal index/AHI ratio; the desaturation index/AHI ratio; the number of > 30% airflow reductions without arousal/the total number of > 30% airflow reductions ratio. An index assessing the respiratory arousal threshold was calculated (Edwards et al., 2014). The cardiac autonomic response to respiratory events was quantified as percentages of changes (20 s after arousal onset) from the baseline (10 s

before arousal onset) in RR intervals, high frequency (HF) and low frequency (LF) power, and LF/HF ratio. Sleep and clinical data were compared between groups using a Kruskal-Wallis test, and autonomic cardiac reactivity data using repeated ANOVA and Student-Newman-Keuls post-hoc analysis.

**Results:** No inter-group difference was found for parameters exploring cortical arousal response nor for the respiratory arousal threshold. The decrease in RR intervals was lower for DRE (6.5%) than DSE (9%, $p < 0.05$) and controls (10%, $p < 0.05$). Epilepsy patients showed a higher early sympathetic response (LF/HF increase: 115% for DRE and 130% for DSE vs 80% for controls, $p < 0.05$). Late parasympathetic activation (HF power increase) was higher in DRE (65%) than DSE (50%, $p < 0.05$) and controls (32%, $p < 0.05$).

**Conclusion:** Although we did not observe an increased post-apnea arousal threshold in OSA patients with versus without epilepsy, our results show an impaired cardiac reactivity with lower arousal intensity in DRE who are at higher risk for SUDEP. Such alteration in autonomic arousal response may be involved in the inability to restore effective ventilation following post-ictal apnea.

**Disclosure**: No

### O205/P787 | Local changes in brain oscillations after stroke

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**Introduction**: Recently, cortical sleep oscillations have been characterized not just as a global phenomenon, but occurring in local regions of the cortex as well. Ischemic stroke disrupts cortical activity, but the effect of these disruptions on sleep oscillations at the local cortical level is unclear.

**Methods**: To study local changes in sleep oscillations, we used wide-field optical fluorescence imaging in mice ($N = 7$) expressing the genetically encoded calcium indicator GCaMP6 in excitatory cortical neurons fitted with plexiglass whole-cortex cranial windows. Sleep was recorded in the head-fixed position prior to, 24 h, 1 week, and 4 weeks after photothrombotic stroke over the left somatosensory (forepaw) cortex. To measure changes in sleep oscillations, multi-taper spectral power was computed in the slow oscillation (<1 Hz) and delta activity (1–4 Hz) frequency range. Zero-lag, seed-based correlations were computed in the slow-oscillation and delta frequency ranges to determine cortical connectivity. One-tailed paired *t*-tests and ANOVAs were used for statistical comparisons.

**Results**: Acutely (24 h) following focal ischemic stroke, slow ($p = 0.0075$) and delta ($p = 0.0040$) oscillation spectral power over and around the ischemic lesion decreased with no change observed contralateral to the stroke or in distant control regions. One week after stroke, slow oscillation power alone increased over and next to the ischemic lesion ($p = 0.044$) that renormalized to baseline levels over 4 weeks ($p = 0.12$). In contrast, delta power remained persistently depressed over the ischemic lesion ($p = 0.013$). Functional connectivity analysis in the slow oscillation range revealed an increase at 24 h after a stroke over the lesion that renormalized over time. In contrast, a persistent loss of delta functional connectivity was observed over the lesion, but increased contra laterally.

**Conclusions**: These results suggest there are local, time-dependent changes in sleep slow oscillations and delta activity after stroke that are accompanied by local changes in cortical connectivity. Manipulating sleep oscillations in a local- and time-specific manner may have clinical utility by altering the course of stroke recovery.

**Disclosure**: No

## 21: MEDICAL DISORDERS AND SLEEP

### O179/P794 | Clinically significant sleep disorders, not shift work status, are associated with mental health in young adults: findings from a representative, population-based Australian cohort study

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**Introduction:** Mental health conditions are a leading contributor to global disease burden in young adults, of whom 25% are shift workers and 20% have a clinically significant sleep disorder. While shift work and sleep disorders have been shown to be independently and prospectively associated with poorer mental health in midlife, the nature of the relationship between shift work, clinical sleep disorders and mental health in young adults is poorly understood. The aim of this study was to determine whether young adult shift workers with a sleep disorder have poorer mental health than those without a sleep disorder.

**Methods:** We used data from the Generation 2, 22-year follow-up of the Raine Study in Perth Western Australia; a longitudinal, population-based cohort of young adults who completed in-laboratory polysomnography (PSG) studies and questionnaires to determine clinically significant OSA (apnoea hypopnoea index $\geq$ 15), chronic insomnia or restless legs syndrome causing distress. Anxiety was measured using the General Anxiety Disorder Questionnaire (GAD-7) and depression with the Patient Health Questionnaire (PHQ-9). Multivariable adjusted robust linear regression models with *M* estimators were conducted. Median (*Md*)and interquartile range (IQR) are reported.

**Results:** A total of 660 young adults (age[y] 21.9 [21.7–22.3], 53% female, employed for 1.6 [0.6–3.3] years) were included. Of these

participants, 27.2% shift workers. Prevalence of at least one clinically significant sleep disorder was similar between shift and non-shift workers (18% *vs*. 21%, $p = 0.51$), and the majority of these disorders were undiagnosed (79% and 81%, respectively). Measures of anxiety ($p = 0.29$) and depression ($p = 0.82$) were not different between shift and non-shift workers; however anxiety and depression scores were higher in those with a clinical sleep disorder than those without (anxiety: 7.0[4.0–10.0] *vs*. 4.0[1.0-6.0]), and depression: (9.0[5.0–13.0] *vs*. 4.0[2.0–6.0]).

**Conclusions:** Clinically significant sleep disorders are common in young shift and non-shift workers. These disorders are predominantly undiagnosed, and presence of at least one sleep disorder is associated with higher depression and anxiety scores. In contrast, mental health scores were similar between shift and non-shift workers. Identifying and treating clinical sleep disorders should be prioritised in young workers, particularly given availability of existing treatment options which may improve mental health.

**Disclosure**: Yes

**Conflict of Interest statement:** ACR reports research support from Safe work SA, Flinders Foundation, Sydney Trains, Compumedics, Teva Pharmaceuticals and Vanda Pharmaceutics which are unrelated to this abstract. RJA reports funding from the National Health and Medical Research Council, the Hospital Research Foundation, Flinders Foundation, ResMed Foundation, Philips Respironics, the Australian Government and Sydney trains which are unrelated to this abstract. BB and SW report research support from Safework SA unrelated to this abstract. JW and KM report research funding from Nyxoah and Incannex Healthcare Ltd which are not related to the content of this abstract. PE reports National Health and Medical Research Council funding related to this abstract. MEC, LS, KS, NM report no conflicts of interest.

## 22: PSYCHIATRIC AND BEHAVIOURAL DISORDERS AND SLEEP

### O036/P196 | Associations between sleep complaints, suicidal ideation and depression among adolescents and young adults in Greece

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**Objectives/introduction:** Depression prevalence increases significantly during adolescence/early adulthood. Depression in youth may present suicidal ideation, while suicide represents the leading cause of death in this age group. Moreover, adolescents/young adults frequently report sleep complaints that may partially be due to depressive symptoms. Studies on the associations between depression, sleep complaints and suicidality in this age group are limited. We aimed to investigate associations between depression, sleep complaints and suicidal ideation in a large ($n = 2771$), representative sample of adolescents (age: 15–17 y $n = 512$) and young adults (age: 18-24 y $n = 2259$) of the general population in Greece.

**Methods:** A telephone structured questionnaire was conducted. Depression was assessed using Physical Health -7 questionnaire, while presence of suicidal ideation and sleep complaints were assessed using the 9$^{th}$ and 3$^{rd}$ question of Physical Health -9 (PHQ-9) questionnaire, respectively. We conducted a direct and indirect effect analysis between the modified PhQ-7 scale, sleep complaints and suicidality controlling for gender, family income, education and substance using mediated (binary) logistic regression models. Collinearity was assessed using correlation matrix test. Analysis was stratified by gender group, that is, adolescents and young adults.

**Results:** In our sample prevalence of suicidal ideation was 7.8%, while 47.9% reported sleep complaints. The mean PhQ-7 score was 6.15 ± 4.11. Regression analysis revealed significant direct paths from depression to sleep complaints (Odds ratio, OR = 1.22 [95% CI 1.19–1.24]//OR = 1.21 [95% CI 1.18–1.24]) and suicidal ideation (OR = 1.18 [95% CI 1.14–1.22 ]//OR = 1.182 [95% CI 1.14–1.22]), as well as sleep complaints and suicidal ideation (OR = 1.82 [95% CI 1.32–2.50] //OR = 1.91 [95% CI 1.33–2.76]) in young adults but not in adolescents. Moreover, we detected a significant indirect effect of depression on suicidal ideation mediated by sleep complaints (18.8%) in young adults.

**Conclusions:** Our findings highlight the presence of complex interactions between subjective psychiatric symptoms and perceived sleep problems accounting, at least in part, for suicidal ideation within young adults but not adolescents. Therefore, treatment of sleep among young adults with depression may significantly independently further reduce suicidal risk.

**Support:** EEA/Norwegian Financial Mechanism 2009-2014, under Project Contract n° EEA Grants/ GR07- 3757

**Disclosure**: No

### O041/P197 | Driving simulator study in depression

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**Introduction:** Depression is characterized by mental, emotional and executive dysfunction, which may have an impact on driving behaviour. Among its symptoms sleep disturbance is very common.

**Methods:** The current study is a comparison of driving simulator performance in patients with depression ($N = 39$) and a group of healthy controls ($N = 30$). Participants were asked to drive on a driving simulator under low (L) and high (H) traffic conditions in an urban (U), a rural (R) and a motorway (MW) scenario. Driving simulator data included speed, lateral movement and safety distance from the preceding vehicle.

**Results:** Speed was found to be negatively correlated with age and female gender. Speed was positively correlated with RLS (UH scenario); surprisingly, a higher Stop Bang score was associated with increased speed. Regarding lateral movement, women seem to be weaving to the left and right less than men on the MW and the UL scenarios. Weaving was correlated negatively with BMI and positively with EPWORTH score in the U scenarios. As regards insomnia symptoms, weaving was positively correlated with AIS score on the MW and negatively in the RH scenario. Safety distance was longer for women and was positively correlated with age (urban and rural scenarios); it was negatively correlated to BMI and to the score of the RLS scale. Being in the patient group and having a higher EPWORTH score was correlated with longer distance from the preceding vehicle across all scenarios. Ability to maintain a constantly stable safe distance was compromised by depression, insomnia symptoms, RLS, Stop Bang score and higher age.

**Conclusion:** Patients with depression kept a higher safety distance than controls; longer safety distance was associated with somnolence. It seems that patients with depression may realize the dangers which come from depression and its symptoms (particularly somnolence) and, thus, they tend to drive more carefully. there are parameters which influence driving behaviour and attitude similarly for both groups (especially age and sex) and specific parameters only for depressed patients (RLS, sleep apnea and insomnia symptoms).

**Disclosure**: No

## O082/P511 | Selective slow-wave sleep disruption differentially modulates cortical excitability in individuals with major depression as compared to healthy controls

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**Introduction:** Individuals with major depressive disorder (MDD) have been posited to have impairments in neuroplasticity, broadly, and deficient cortical excitability, specifically. Because slow-wave sleep (SWS) has been implicated in the homeostatic regulation of neuroplasticity, it is possible that modulating SWS may serve to alter cortical excitability and lead to downstream changes in mood. Therefore, in this study we aimed to selectively suppress SWS and examine its impact on cortical excitability in both individuals with major depression (MDD) and healthy controls.

**Methods:** 16 individuals (9 F) with MDD and 9 (6 F) healthy controls have been recruited to date for an ongoing clinical trial. Slow-wave sleep was disrupted (SWD) utilizing auditory stimulation on one of two overnight sleep laboratory visits conducted one week apart (Baseline, SWD). Cortical excitability was assessed in the morning following each overnight visit using motor evoked potentials (MEP) generated from transcranial magnetic stimulation (TMS). Correlational analysis was used to explore the relationship between percent N3 sleep and cortical excitability. Repeated measures ANOVA was used to evaluate the change in MEP amplitude following SWD with condition (Baseline, SWD) as the within-subject factor and group (MDD, HC) as the between-subjects factor.

**Results:** Results indicated that for HC, a greater percentage of N3 at baseline was associated with lower cortical excitability at baseline, $r = -0.93$, $p = 0.002$, however this association did not meet statistical significance for those with MDD or for HC following SWD. ANOVA results revealed a significant Condition x Group interaction ($F(1,23) = 6.45$, $p = 0.018$) for change in MEP following SWD. While not all post-hoc $t$-tests reached statistical significance due to low power, results indicated that while HC showed a significant decrease in cortical excitability, $t(8) = 2.23$, $p < 0.05$, individuals with MDD demonstrated a descriptive increase, $t(15) = -1.58$, $p = 0.07$.

**Conclusions:** These preliminary results from ongoing data collection provide in-vivo evidence of an association between cortical excitability and the amount of SWS during the preceding sleep period in HC. We also demonstrate that SWD produces a unique pattern of response in cortical excitability in individuals with MDD in contrast to HC. This may indicate that SWS functions in a fundamentally different way in MDD.

**Disclosure**: No

## O100/P512 | Assessing the role of sleep and circadian features in predicting depression-related outcomes in UK Biobank using penalised regression

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**Introduction:** Sleep and circadian disruption are risk factors for the onset and severity of depression. It remains unclear, however, which features of sleep and circadian rest-activity function are the most important predictors of depression-related outcomes, and whether measurement of such features can identify individuals at greater risk of depression or more severe depression outcomes.

**Methods:** Within a subset of the UK Biobank cohort who provided both objective actigraphy data and baseline subjective sleep characteristics ($n = 83{,}826$), we used penalised regression machine learning techniques to identify which of 43 subjective and objective sleep/rest-activity characteristics were the most useful predictors of depression-related outcomes. Outcomes included history of Major

Depression (MD) versus, non-MD controls, and seven MD dimensions reflecting increased severity, for example, presence versus, absence of: atypical symptoms (hypersomnia and weight gain); comorbid anxiety; and suicidality. Lasso, ridge, and elastic net models with 10-fold nested cross-validation were conducted for each outcome with the 43 sleep/rest-activity characteristics and with age, sex, and Townsend deprivation score as predictors. The model showing highest Receiver Operating Characteristic Area Under the Curve (AUC) in the test data was chosen, and selected features examined.

**Results:** For MD versus, controls ($n = 64{,}883$), lasso was the best performing model (AUC 0.68, 95% confidence interval (CI) 0.67–0.69). Selected features included subjective difficulty getting up, insomnia, a sleep disorder diagnosis, and actigraphy-measured daytime inactivity. These features were selected across most models, although discrimination was typically poor (AUC < 0.7). Discrimination was reasonable for atypical vs. typical symptoms ($n = 19{,}680$; ridge regression: AUC = 0.74, 95%CI 0.71–0.77). Top features again included difficulty getting up and daytime inactivity, as well as sleep duration.

**Conclusions:** Sleep and circadian measures alone did not discriminate those at increased risk of depression or more severe depression, but may be useful in highlighting the most prominent sleep/rest-activity related risk factors. Subjective difficulty getting up, insomnia, and daytime inactivity were commonly associated with worse depression-related outcomes and may be specific targets for intervention. Future studies will examine whether combining these features with sociodemographic, lifestyle and genetic predictors can identify those at greatest risk of poor depression outcomes.

**Disclosure**: No

## O101/P513 | Effects of selective slow wave sleep deprivation on mood in depressed adolescents: Preliminary findings

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**Objectives:** There is an urgent need for safe, rapid-acting antidepressant strategies for depressed youth. Among depressed adults, initial studies show that selective slow wave sleep deprivation (SW-SD) acutely improves depression without disrupting sleep duration, but this approach remains untested in youth. In depressed adolescents (13–18 y), we are conducting a pilot study evaluating the antidepressant effects of SW-SD.

**Methods:** Fifteen adolescent participants in a depressive episode ($N = 15$; Mean Age = 16.87 y; 12 Females) completed 3 consecutive nights of overnight polysomnographic sleep monitoring: Baseline (Night 1), Selective Slow-Wave Sleep Deprivation via acoustic stimulation (SW-SD; Night 2), and Recovery (Night 3). Participants and clinical raters were told that participants were allocated to SW-SD or a Sham condition on Night 2; however, all participants received SW-SD on Night 2. After each night, clinician-rated depression severity was assessed with a modified Child Depression Rating Scale, and participants rated specific psychological processes that contribute to elevated negative affect (rumination; Ruminative Response Scale) and blunted positive affect (anhedonia; Snaith-Hamilton Pleasure Scale) in depression. Linear mixed-effects models adjusted for age, sex, SSRI medication, and baseline depression severity.

**Results:** There was a significant effect of night (Baseline vs. SW-SD vs. Recovery) on slow wave sleep percentage (SWS%; $F_{1,10} = 71.4$, $p < 0.0001$). SWS% was significantly lower on the night of SW-SD relative to Baseline ($p < 0.0001$) and Recovery ($p < 0.0001$), but SWS on Baseline and Recovery nights did not differ ($p = 0.827$). SW-SD did not significantly affect sleep duration ($p > 0.1$) or the amount of rapid-eye movement sleep ($p > 0.1$). While clinician-rated depression severity improved from Baseline to SW-SD in 8 out of 15 participants (53%), there was no significant effect of night on clinician-rated depression severity ($F_{1,10} = 0.9$, $p = 0.91$). SW-SD resulted in a reduction in rumination relative to Baseline ($F_{1,10} = 3.73$, $p = 0.04$), but not for anhedonia ($F_{1,10} = 1.01$, $p = 0.37$).

**Conclusions:** Preliminary findings indicate that SW-SD may acutely improve rumination overnight in depressed adolescents, but not overall depressed mood or anhedonia. If these initial findings are upheld, data would support further evaluation of SW-SD as strategy for targeting specific psychological processes, like rumination, in adolescents. Data collection for this study is ongoing, including resting-state fMRI before and after SW-SD.

**Disclosure**: No

## O102/P514 | Predictors of suicidal ideation and preparatory behaviors in individuals with bipolar disorder: the potential contribution of chronobiological dysrhythmicity and of its association with hopelessness

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Bipolar disorder (BD) is the sixth leading cause of disability among all illnesses worldwide; premature mortality has been identified being related to the very high risk of suicide in BD. Whereas risk factors for suicidal behaviors are multiple and complex, hopelessness appears to be a major independent risk factor. Compelling evidence has also demonstrated that BD is frequently associated with circadian rhythm alterations, contributing to risk of suicidal behaviors in BD. Although hopelessness and circadian rhythm alterations both contribute to suicidal risk in BD, a paucity of research has examined how these factors are interrelated and how they are associated with suicidal risk in BD.

**Methods:** One hundred twenty-seven patients (77 females, mean age of 47.4 ± 12.5 years) with a major depressive episode and bipolar disorder (BD) type I or II (Structured Clinical Interview for DSM-5) were recruited and assessed for depressive and manic symptoms (Beck Depression Inventory-II, Young Mania Rating Scale) and with the Biological Rhythms Interview of Assessment in Neuropsychiatry, Beck

Hopelessness Scale, and Scale for Suicide Ideation. Univariate regression and mediation analyses were performed.

**Results:** Forty-one patients (32.3%) showed clinically significant suicidal ideation and were more frequently affected by BD type I ($p = 0.029$) with mixed features ($p = 0.022$). Compared to nonsuicidal individuals, they had significantly more depressive symptoms ($p = 0.019$), higher emotional component of hopelessness ($p = 0.037$), and higher dysrhythmicity of sleep ($p = 0.009$), activities ($p = 0.048$), and social life ($p = 0.019$). Passive and active suicidal ideation and suicidal plans were correlated with the dysrhythmicity of sleep and social life. Dysrhythmicity of sleep and social life mediated the direct effect of depressive symptoms on passive and active suicidal ideation and also of active ideation on suicidal plans.

**Conclusions:** Chronobiological alterations directly contributed to passive and active suicidal ideation and to suicidal preparation, with a key role of dysrhythmicity of sleep, activities, and social life. Chronobiological alterations also impacted the emotional component of hopelessness, hence indirectly contributing to suicidal ideations and plans. These findings call for the systematic screening of these dysrhythmicity dimensions when considering suicidal risk in individuals with BD.

**Disclosure**: No

## O103/P515 | REM sleep behavior disorder in patients with post traumatic stress disorder

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**Objectives:** This study is part of a larger randomized controlled trial. We wish to assess the prevalence of probable REM Sleep Behavior Disorder (pRBD) diagnosed by REM Sleep Disorder Questionnaire (RBDSQ) in a group of 219 refugees diagnosed with Post Traumatic Stress Disorder (PTSD). We wish to evaluate the significance of pRBD on the patient's subjective sleep disturbances and level of functioning and evaluate the significance of pRBD on the outcome of the PTSD treatment. By combining our data with data from a minor PSG-study, we wish to give an approximation of the 'true' prevalence of RBD.

**Methods:** 219 refugees diagnosed with PTSD and suffering from sleep disturbances were included. They were assessed prior to and after treatment using several validated questionnaires: The Pittsburg Sleep Quality Index (PSQI), Disturbing Dreams and Nightmares Severity Index (*DDNSI*), REM Sleep Behavior Disorder Screening Questionnaire(RBDSQ), Sheehan Disability Scale (SDS) and WHO Disability Assessment Schedule 2.0 (WHODAS). At the same center 20 different PTSD patients participated in a smaller study examining sleep by polysomnography (PSG).

**Results:** Of the 219 patients enrolled in this study 125 (57%) fulfilled criteria for pRBD, while 51 (23%) did not (nonRBD) and 43 (20%) were non-responders. Of the pRBD patients 67% experienced weekly nightmares compared to 20% in the nonRBD group. The pRBD patients were more impaired by their nightmares than the nonRBD patients as measured by DDNSI. An OLS regression model was used to analyze change in questionnaire scores from baseline to follow-up. At follow-up pRBD was significantly correlated with a worse outcome on PSQI, with no difference between groups regarding WHODAS, SDS and DDNSI. Regarding the PSG-study, 12 out of 20 PTSD patients fulfilled criteria for pRBD (60%) of these one patient had REM Sleep Without Atonia (RSWA) as measured by PSG.

**Conclusions:** pRBD is frequent in PTSD patients. PTSD patients with pRBD have more nightmares and are more impaired by these than nonRBD patients. pRBD is correlated with a worse treatment outcome assessed by PSQI. RBD symptoms seem not to be related to findings of RSWA thereby not fulfilling diagnostic criteria for "true" RBD.

**Disclosure**: No

## O104/P516 | Psychological and biological risk factors for insomnia and depressed mood among hospital nurses working in shifts

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**Objectives:** This study examines the contribution of common biological and psychological risk factors in the development of insomnia and depressed mood and aims to develop a novel psychobiological conceptual model to describe their co-occurrence among hospital nurses working in shifts. The theoretical framework for this study is based on the Behavioral Model for Insomnia and the Analytical Rumination Hypothesis for Mood and Depression. The latter model is novel in that it conceptualizes rumination and depressed mood as adaptive behavioral features in the context of stressful situations.

**Methods**: In this cross-sectional design, we recruited female hospital nurses, shift and day workers, and assessed them for insomnia, depressed mood, stress, analytical rumination and chronotype by validated self-administered questionnaires delivered online. Using SEM, we assessed common pathways between psychological and biological factors affecting insomnia and depressed mood.

**Results**: 448 nurses filled out the electronic questionnaires. Shiftwork nurses ($n = 358$) compared to day-work nurses ($n = 90$) were found to have higher rates of insomnia and depressed mood (70.1% vs. 52.2% and 45.8% vs. 30%, respectively). Shift nurses reported higher levels of insomnia ($p < 0.001$), depressed mood ($p = 0.001$), stress ($p = 0.033$), and a tendency to an evening chronotype

($p < 0.001$) compared to day-work nurses. A positive linear relationship was found between insomnia and depressed mood in both shift nurses ($r = 0.527$, $p < 0.001$) and day-work nurses ($r = 0.534$, $p < 0.001$). SEM showed that shift work contributed directly to insomnia but indirectly to depressed mood. Chronotype and stress mediated the associations between shift work and both insomnia and depressed mood. Analytical rumination, stress, and evening chronotype were directly associated with insomnia and depressed mood.

The overall model showed a good fit between the empirical and theoretical model proposed in the study [$\chi^2(4) = 0.16$, $p = 0.060$, CFI = 0.99, RMSEA = 0.053].

**Conclusions**: Understanding factors underlying insomnia and depressed mood among shift-working nurses, who are particularly vulnerable to develop these disorders, is a first step towards developing interventions aimed at improving nurses' health and quality of life, which in turn improves the quality of care provided to patients. This study provides the groundwork in creating a theoretical psychobiological model to examine these phenomena in hospital nurses.

**Disclosure**: No

## 23: NORMAL PHYSIOLOGY OF SLEEP AND NORMAL VARIANTS

### O020/P201 | Sleep duration effect on heart and respiratory rate in a large US sample

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**Objectives:** To examine the effect of sleep duration on heart rate (HR) and respiratory rate (RR) in a large U.S. sample of users of a home-based under-mattress monitoring device.

**Methods:** Sleep data from 76,769 users with 14,296,394 total recorded nights from January 4, 2021 to March 3,2022, were collected through a commercially-available home-sleep monitoring-device (Sleeptracker-AI Monitor, Fullpower Technologies, California, USA). The device passively monitors sleep using piezo-electric sensors that register the forces exerted through the mattress. Only subjects with at least 300 nights of recordings during the period were included. In total 18,252 individuals (40% female, 13% unspecified gender, mean age 49) with 5,846,745 recorded nights met this inclusion criterion. Estimated total sleep time (TST) was categorized as one of: <5 h, 5-6 h, 6–7 h, 7–8 h, 8–9 h and ≥9 h. Normalized HR and RR for a recording were taken to be the mean HR and RR for that recording as a percentage of the average over all recordings for that subject. Excess HR and RR for a recording was taken to be the excess/deficit of the normalized HR and RR over 100%.

**Results:** The mean (standard deviation [SD]) across subjects' average HR values was 63.5 (7.2). For each TST category (<5, 5–6, 6–7, 7–8, 8–9, >9 h), the average, across subjects, of the excess HR was: +1.02%* [+0.94,+1.09], +0.53%* [+0.49,+0.57], −0.00% [−0.03,+0.02], −0.21%* [−0.23,−0.18], −0.04% [−0.08,+0.00], +0.43%* [+0.35,+0.51]. Regarding RR, the mean (SD) across subjects' average RR values was 15.3 (2.2). For each TST category, the average, across subjects, of the excess RR was: +0.39%* [+0.33,+0.45], +0.22%* [+0.19,+0.25], -0.00% [−0.02,+0.02], -0.11%* [−0.12,−0.09], −0.01% [−0.05,+0.02], +0.30%* [0.23,0.36]. Throughout, an * indicates statistically significantly different from 0% at the $p < 0.05$ level.

**Conclusion:** Subjects had lower HR and RR than their average on nights when they slept 7–8 h. Interestingly, their HR was higher than average on nights when they slept <6 h or ≥9 h. Notably, the American Academy of Sleep Medicine recommends ≥7 h of sleep, without an upper limit. Furthermore, these findings may inform on the relationship between extreme sleep duration as a risk factor for cardiovascular events.

**Disclosure**: No

## 24: PAEDIATRICS

### O018/P209 | An automated analyses approach reveals the expected spike-wave dependent impairment of the recovery function of sleep in a large-scale pediatric patient group

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**Introduction:** Electroencephalography (EEG) slow waves are an electrophysiological marker of the recovery function of sleep. In certain pathological conditions, such as different types of epilepsy, slow waves are affected by epileptiform discharges forming so called "spike waves". Bölsterli et al. have previously provided evidence that the recovery function of sleep is impaired under these conditions. Here we applied an automated approach to extend the analysis to different pediatric patient groups, and to investigate this impairment of sleep recovery in a large-scale data set.

**Methods:** Machine learning methods based on artificial neural networks were developed for automatic spike and sleep detection in pediatric patients. A data set available at University Children's Hospital Zurich contains approximately 30'000 EEG recordings of children with suspected epilepsy diagnosis (acquired in the past > 20 years), out of which we identified 682 recordings of interest (sleep episodes >4 h). Sleep recovery was assessed in these patients as a change in the slope of slow waves from the first to the last hour of sleep. Spike-wave index (SWI) was calculated as the number of spikes per sleep time.

**Results:** The algorithm successfully identified spikes and sleep with high performance (Cohen's kappa coefficient = 0.72 and 0.71, respectively). The slope change across the night negatively correlated with SWI ($R = -0.28$, $p < 0.001$), and this was most pronounced for Lennox-Gastaut syndrome ($R = -0.52$, $p = 0.01$). Further, the slope of slow-waves in the first and last h of sleep negatively correlated with age ($R = -0.35$ and $R = -0.33$, $p < 0.001$).

**Conclusions:** The good performance of the automatic algorithms allowed us to replicate major findings about sleep recovery in patients and during development in a large-scale data set: (1) the higher the SWI the more sleep recovery is impaired, and this is especially pronounced in Lennox-Gastaut syndrome; (2) the slope of slow waves decreases with increasing age.

**Disclosure**: No

## O022/P210 | Co-modulation of awake theta power and habitual sleep across the first 3 years of life in infants at elevated likelihood for ASD/ADHD

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**Introduction/Objectives**: Disordered sleep is a symptom of Autism-Spectrum-Disorder(ASD) and Attention-Deficit-Hyperactivity-Disorder(ADHD). Research has yet to clarify if and how early sleep patterns contribute to the development of ASD/ADHD symptomatology. Theta band oscillations (3-6Hz) are a marker for brain development and predict non-verbal cognitive abilities in infants at elevated likelihood for ASD (Jones et al., 2020).

Using a prospective sibling design in our study aim to understand how parent-reported sleep relates to ASD/ADHD outcome scores and an EEG indicator of brain development (theta power) across the first three years of life in infants at elevated likelihood of ASD/ADHD.

**Methods:** $N = 166$ Infants participated in this study. Infants at low ($N = 29$) and elevated likelihood for ADHD($N = 32$)/ASD($N = 80$)/ASD+ADHD($N = 20$) were tested at ages 5, 10, 14 months for parent-reported sleep (Sleep and Settle Questionnaire; Matthey, 2001) and 5, 10, 14 and 24 months for EEG while watching 60-s videos of toys and nursery rhymes (124-channel, EGI). ASD/ADHD symptoms were measured at 36 months with SRS2/ADOS2/ADI-R. Analyses were pre-registered under https://osf.io/pq32t and theta band frequencies and change parameters were extracted (see: Braithwaite et al., 2020). We used GEEs to analyse sleep data in association with outcome data, and pending pre-registration approval random-intercept cross-lagged panel models to investigate longitudinal associations between theta and sleep.

**Results:** Infants with elevated likelihood of ASD showed less night sleep compared to the other groups [$F(1,133) = 10.08$, $p = 0.002$, $np^2 = 0.07$]. Infants with an elevated likelihood of ADHD [$F(1,133) = 0.17$, $p = 0.68$, $np^2 = 0.001$] did not show this. There was no association of 36m ASD/ADHD traits with day sleep in either group (ASD: [$F(1,132) = 0.29$, $p = 0.59$, $np^2 = 0.002$], ADHD:[$F(1,132) = 2$, $p = 0.16$, $np^2 = 0.01$]). ASD outcome analyses show same pattern. Additional results on theta and sleep will be presented.

**Conclusion:** Our preliminary results show lower parent-reported night sleep could be specific to ASD but not ADHD, tentatively highlighting sleep duration as a potential early intervention target. Cross-lagged panel models will clarify how this finding associates with our EEG marker of brain development (theta power) in this cohort. Our longitudinal study enables us to disentangle the potential cascading and concurrent effect of different aspects of sleep on brain development markers and on symptomatology of neurodevelopmental disorders.

**Disclosure**: No

## O023/P211 | Multi-trajectory modelling of children' sleep characteristics between 1 and 5.5 years in the French ELFE birth-cohort

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**Introduction:** Early sleep disturbances are associated with short- and long-term health problems. Most studies report sleep disturbances separately, whereas they may be related. We aimed at identifying groups of children in a birth-cohort with similar sleep characteristics evolution between 1 and 5.5 years of age.

**Method:** The French ELFE birth-cohort included 18,327 newborns in 2011. Sleep information (night (NSD) and daytime (DSD) sleep durations, sleep onset difficulties (SOD), night-waking (NW)) was collected by interviews at ages 1, 2, 3.5, and 5.5 years. DSD was collected until age 3.5 years. Sleep multi-trajectories were identified using group-based trajectory modelling. Children were assigned to the group of multi-trajectories where they had the highest probability of belonging.

**Results:** We identified 5 groups of 1–5 y multi-trajectories from 9,237 children with sleep data available at least 2 of the 4 time-points. The first group (G1, 31.6%) showed a mean NSD between 10 and 11 h, a decreasing mean DSD from 3 h12 to 1 h36, a stable low SOD prevalence (≈5%), a decreasing NW prevalence (from 14% to 2%). The second group (G2, 10.3%) showed a mean NSD ≥11 h00, a steeply decreasing mean DSD from 4 h00 to 1 h42, a low SOD prevalence at age 1 y (2%) increasing to a peak of 18% at age 3.5 y, a stable NW prevalence (≈10%). The third group (G3, 31.0%) showed a mean NSD between 11 and 11 h45, a decreasing mean DSD from 2 h36 to 1 h30, stable NW and SOD prevalence (≈10%). The fourth group (G4, 9.6%) showed an increase in NSD from 8 h30 at age 1 y to a plateau of ≈10 h30 thereafter, a decreasing mean DSD from 3 h00 to 1 h30,

high and decreasing SOD (from 40% to 20%) and NW (from 50% to 10%) prevalence. The fifth group (G5, 17.5%) showed a stable mean NSD (≈10 h30), a decreasing mean DSD from 2 h30 to 1 h30, a high SOD prevalence (≈35%) with a peak of 50% at age 3.5 y, a high decreasing NW prevalence (from 40% to 18%).

**Conclusion:** We identified groups with different sleep characteristics evolution between 1 and 5.5 years of age. Specific associated factors identification is ongoing.

**Disclosure**: No

## O024/P212 | Parents' sleep multi-trajectory modelling between 3 and 36 months postpartum in the sepages cohort

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**Introduction:** Child birth is known to alter parental sleep. However, few study considered both parents, mostly focusing on maternal and child sleep. We aimed at identifying multi-trajectories including night sleep duration (NSD), nap duration (ND) and subjective sleep loss (SSL) reported by both parents between 3 and 36 months postpartum in the SEPAGES cohort.

**Methods:** The SEPAGES cohort included 484 pregnant mothers and 410 fathers in Grenoble area, France. Parental sleep information was collected by self-administered-questionnaires at 3, 18, 24 and 36 months postpartum. Group-based trajectory modelling was used to identify multi-trajectories. The best model was selected based on Bayesian Information Criteria and verified according to the recommended criteria. Each couple was assigned to the group of multi-trajectories where they had the highest probability of belonging.

**Results:** From 188 couples reporting sleep data at least 2 times across the 4 time-points, we identified 3 groups of sleep multi-trajectories between 3 and 36 months. The first group (G1, 29.3%) was characterized by a mean maternal and paternal NSD of 8–9 h, a stable mean maternal and paternal ND (≈10 min and ≈5 min, respectively), a decreasing maternal SSL (58% to 31%) and a stable paternal SSL (≈30%). The second group (G2, 27.7%) was characterized by a stable mean NSD of 7–8 h for both parents, a decreasing maternal mean ND from 41 to 23 min between 3 and 18 months then remaining stable, a stable paternal mean ND (≈10 min) and high SSL for both parents (90% to 86% for mothers and 76% to 61% for fathers). The third group (G3, 43.0%) was characterized by similar sleep patterns for both parents: a mean NSD of 8–9 h, a relatively long mean ND, decreasing from 54 to 41 min for mothers but increasing from 28 to 39 min for fathers, and a stable but relatively high SSL (≈70% for mothers and ≈55% for fathers).

**Conclusions:** We identified specific post-partum parental sleep pattern evolutions. Thus, child birth may have different mid-term consequences on both parents' sleep. Identification of parental and child associated factors with each group is ongoing.

**Disclosure**: No

## O025/P213 | The long-term effect of adenotonsillectomy on changes of position during sleep in pediatric obstructive sleep apnea

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**Objective/Introduction:** Although adenotonsillectomy is known to influence on position change behavior during sleep, the data are limited to short-term follow up results. This study aims to evaluate long-term effect of adenotonsillectomy on changes of position during sleep in pediatric obstructive sleep apnea (OSA).

**Methods:** Children with snoring or sleep apnea who underwent nocturnal standard polysomnography and adenotonsillectomy were retrospectively analyzed in this study. The preoperative and postoperative differences in the frequency of positional changes during sleep and the distribution of sleep positions were investigated.

**Results:** A total of 20 pediatric patients (mean age = 6.6 ± 3.4 years; male: female = 15: 5) with OSA were included. The mean follow up duration between the preoperative and postoperative polysomnography was 54.5 ± 22.3 months. The respiratory parameters including AHI, minimal oxygen saturation were improved. The total number of positional changes during sleep and positional change index significantly (9.7 ± 5.0 [Pre-op] vs 4.1 ± 2.9 [Post-op]; $p < 0.001$) decreased after adenotonsillectomy. There was a statistically significant increase in the proportion of sleep time spent in supine position (40.0 ± 19.0% [Pre-op] vs 57.2 ± 32.0% [Post-op]; $p = 0.023$) on long-term follow up.

**Conclusion:** The tendency to decrease in the frequency of positional changes and increase of supine position proportion during sleep was maintained in long-term follow up after adenotonsillectomy in pediatric OSA.

**Disclosure**: No

## O026/P214 | Sleep health characteristics among an underrepresented iranian population: Children with cerebral palsy and their caregivers

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**Objectives:** Cerebral palsy (CP) is the most common cause of disability in childhood. Sleep disorders in children with CP affect the quality of life of the child and other family members. The aim of this study was

to investigate the types of sleep problems in children with CP and its association with sleep quality of their caregivers.

**Methods:** This was a cross-sectional study conducted in occupational therapy centers in city of Tehran in 2020–2021. Children with known CP ages between 4–12 years who were referred to occupational therapy clinics for rehabilitation, primary caregiver were included. Their caregiver completed three questionnaire consisted of Children Sleep Habit Questionnaire (CSHQ), Gross motor function classification system (GMFCS) and Pittsburgh Sleep Quality Index questionnaire (PSQI).

**Results:** Current study included 153 children with CP; ages 4–12 years. An abnormal total CSHQ score (>41) was found in 94.8% of children with CP. Sleep breathing disorders score was significantly higher in school-age children. Daytime sleepiness was significantly higher in girls. Duration of sleep, sleep breathing disorders, and total score of CSHQ were significantly higher in higher levels of GMFCS. Children with epilepsy had significantly higher sleep resistance score than those without. 84.9% caregivers had poor sleep quality. Caregivers with poor sleep quality, had children with more sleep anxiety and parasomnia. Pearson's chi-squared test was used for categorical variables and *t*-test was used for quantitative values. Regression was used to analyses predictors of child sleep and caregiver's sleep quality. Data were analyzed in SPSS v 26. *p*-Values less than 0.05 was considered significant.

**Conclusions:** Children with CP suffer from higher prevalence of sleep disorders. Higher disability and presence of epilepsy increases chance of sleep disorders among these children indicating a need for more attention on this subpopulation. We showed that parents' poor sleep quality is associated with prevalence of sleep problems in these children.

**Disclosure**: No

## O027/P215 | "Easier said than done". Family sleep arrangements during the first two years of a baby's life

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**Introduction:** Bedsharing (BS) between mother and baby is widely questioned by health authorities despite being associated with important benefits, such as longer duration of breastfeeding (BF). Hence, BS often occurs as an undisclosed and unplanned practice, which may imply risks and compromise its benefits.

**Objective:** To assess parents' expectations and planification about night-time sleeping arrangements, their actual adherence to the official recommendations and how this relates to the duration of (BF).

**Methods:** We analysed the responses of 3300 mothers to a survey distributed through internet, health centres and educational centres, asking where they planned for and where their baby finally slept, the reason for BS if it was done, and the duration of BF. Sample characteristics were described, and survival analyses were applied to the duration of BF using the Kaplan-Meier function and lonk-rank test.

**Results:** A high percentage of bedsharing was observed during the first two years of life (60.1% in the first three months, 54.8% for the second year), most of which was unplanned (only 14.9% in the first three months and 11.6% in the second year was planned), with significant differences ($p < 0.001$ at both times). There are significant differences in the duration of BF when BS is practised along the first two years (*p*-value < 0.001). Pre-planned and/or satisfying BS is associated with longer duration of BF ($p < 0.001$).

**Conclusions:** Families try to adapt to the official recommendations, but only a minority succeeds. The relationship of BS to the total duration of BF is clear, even if BS has not been planned. We know that the natural behaviour of the human species is for mother and baby to sleep in intimate contact, and these data reflect that the closeness between mother and baby takes place even against official recommendations and initial plans. It is imperative, therefore, that health personnel and authorities take this reality into account when designing their official recommendations and, in particular, when addressing and dealing with the infant sleep problems characteristic of a society that has normativised the solitary sleep of babies, which clearly undermines BF, that is so important for maternal and infant health.

**Disclosure**: No

## O028/P216 | Sleep disorders in children with celiac disease and the effect of therapy

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**Background and objectives:** Celiac disease (CD) is an immune-mediated enteropathy initiated by gluten ingestion in genetically susceptible individuals. The clinical spectrum of CD is remarkably wide with intestinal and extra intestinal features including neuropsychiatric manifestations. While studies of adults with CD have shown high rates of sleep disturbances there is limited data in children. Our objectives were therefore to assess the association between sleep disturbances and CD in children, and the effect of a glucose-free diet (GFD) on these complaints.

**Methods:** A prospective longitudinal study. Parents of children three to twelve years old, referred for endoscopy, were enrolled and completed two questionnaires: the Sleep Disturbance Scale for Children (SDSC) and modified Sleepiness Scale for children (mESS). Children with CD were compared with healthy controls and children with abdominal pain but no abnormal findings on investigation (AP). Parents of children with CD and children AP, were contacted 6 months after diagnosis for follow up.

**Results:** A total of 101 subjects participated with a mean age of 6.5 (2.8), 51% female, 38 with a final diagnosis of CD, 18 RAP, and 45 healthy controls. SDSC total scores were 37.4 (8.7), 41.3 (11.3) and 45.4 (13.7) in healthy controls, children with CD and AP respectively ($p = 0.024$). There was a significant difference in the disorders of arousal domain ($p = 0.044$). there were no significant differences on the mESS. No improvement was seen after 6 months on a GFD other than a trend in children with celiac disease and abdominal pain on presentation.

**Conclusions:** In this first prospective study of sleep disturbances in children with CD, we show high rates of disturbed sleep compared with healthy children. Sleep disturbances did not improve on a GFD but may be driven by abdominal pain. We suggest that CD be included in the evaluation of children presenting with sleep complaints.

**Disclosure**: No

## O029/P217 | Restless sleep disorder in children with epileptic and non-epileptic nocturnal attacks

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**Introduction:** Restless sleep disorder (RSD) is a sleep disorder recently defined in children. The comorbidity of RSD in patients with other sleep-related disorders/events remains to be elucidated. We aim to investigate the frequency and the characteristics of RSD among children with epileptic and non-epileptic nocturnal attacks.

**Methods:** We prospectively evaluated all children (<18 years) having a full-night polysomnography recordings who were referred for evaluation of sleep-related epilepsy or non-epileptic nocturnal events and restless sleep. The presence of RSD, index of large muscle group movements (LMM) and cyclic alternating pattern (CAP) analysis, and heart rate variability (HRV) were evaluated.

**Results:** A total of 34 children included. From these 9 (26.5%) had nocturnal epilepsy, 10 (29.4%) had non-epileptic nocturnal paroxysmal events consistent with NREM-related parasomnia and 15 children (44.1%) were not found to have any nocturnal events. LMM index in epilepsy group was 5.0 $\pm$ 3.6/h, 3.3 $\pm$ 1.8/h in parasomnia group ($p = 0.068$, between patients with epilepsy and parasomnia), 3.6 $\pm$ 2.8/h in NOS group ($p =$ n.s.). Mean index of LMM associated with arousal was 3.8 $\pm$ 3.1/h in epilepsy, 2.1 $\pm$ 1.5/h in parasomnia ($p = 0.053$, between patients with epilepsy and parasomnia), 2.5 $\pm$ 3.0/h in NOS group ($p =$ n.s.). Nine children fit criteria for RSD (44.4% in epilepsy, 20% in parasomnia and 20% in NOS group). Mean CAP cycle was 63.0 $\pm$ 28.2 in epilepsy, 53.2 $\pm$ 14.8 in parasomnia ($p = 0.009$, between patients with epilepsy and parasomnia), 49.0 $\pm$ 25.2 in NOS group ($p =$ n.s.). Mean index of A3 type was significantly higher in epilepsy group in comparison to parasomnia group ($p = 0.040$). The comparison of the patients with RSD in each group showed that the mean duration of A2 type was highest in NOS group ($p = 0.030$), while other parameters did not show significant differences. In HRV analysis, LF/HF ratio in NREM sleep was highest in NOS group, followed by epilepsy group, and it was lowest in the children with parasomnia ($p = 0.034$).

**Conclusions:** Restless sleep disorder is found in higher frequency in children with epileptic and non-epileptic nocturnal events. RSD can be a contributor to sleep disruption in these children. Central pattern generators have been postulated as a common pathophysiologic mechanism in epilepsy, parasomnia and sleep movement disorders but further research is needed.

**Disclosure**: No

## O086/P525 | Differential effects of arousals on the heart rate surge at respiratory event termination in preterm and term born children with sleep disordered breathing

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**Background:** The repetitive surges in heart rate (HR) and blood pressure (BP) at respiratory event termination underpin the elevated BP and altered autonomic HR control associated with sleep disordered breathing (SDB). As children born preterm are at greater risk of adverse cardiovascular outcomes, we aimed to determine whether the HR response to obstructive respiratory events was elevated compared to children born at term.

**Methods:** Fifty children aged 3–12 years born preterm (<37 weeks of gestational age), were matched for SDB severity, age and gender with term born children. Beat-beat changes in HR were compared between a 10 s baseline before respiratory events to early, late event, and 15 s post event during NREM and REM sleep and between events terminating with and without arousal.

**Results:** 1,203 obstructive events (60 apnoeas, 1143 hypopneas) were analysed. During NREM, HR was lower in the preterm group in all event phases, (Baseline: Preterm median 83 bpm [IQR 76,92], Term 89 bpm [82,98]; Late Event: Preterm 78 bpm [71,85], Term 83 bpm [75, 90]; Post Event: Preterm 101 bpm [93,109], Term 106 bpm [98,114]; $p < 0.05$ for all) but the increase in HR post-event was similar, with the exception of events terminated by arousal, when a greater change was seen in the preterm group (Preterm 23% [12,34], Term 18% [10,29]; $p < 0.05$).There were no differences during REM sleep or after events without arousal.

**Conclusion:** The greater magnitude of surges in HR following respiratory events terminated with an arousal, which occur repeatedly throughout the night, may contribute to adverse cardiovascular outcomes in preterm born children with SDB.

**Disclosure**: No

O176/P811 | **Increased prevalence of depression, but not of insomnia and anxiety, during the initial phase of the COVID-19 pandemic: a longitudinal study among high school students**

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**Objectives:** There has been much concern about the impact of the COVID-19 pandemic and associated social restrictions on adolescent health. The aim of the present study was to compare symptoms and prevalence rates of insomnia, anxiety and depression between pre-pandemic times and the initial phase of the COVID-19 pandemic, in a large sample of Norwegian adolescents.

**Methods:** The longitudinal survey was conducted in a large sample of high school students (16–17 years old), and included the Bergen Insomnia Scale (BIS), the General Anxiety Disorder-7 (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9). Wave 1 was conducted in spring 2019 and wave 2 in spring 2020, during the last 10 days of a 60-day long, COVID-19-related, school lockdown period. A total of 2249 students responded in both survey waves, representing 60.2% of the invited cohort. Statistical analyses included paired-samples *t*-tests and McNemar's tests, the latter with dichotomous proxies of insomnia disorder (based on BIS) and anxiety/depression (GAD-7/PHQ-9 scores ≥10, indicating moderate to severe symptom levels) as dependent variables.

**Results:** The BIS score was slightly reduced from 12.3 ± 8.4 in 2019 to 11.9 ± 8.2 in 2020 ($p = 0.028$), but the prevalence rate for insomnia remained stable (33.4% vs. 33.6%, $p = 0.896$). Similarly, the GAD-7 score was reduced from 5.9 ± 4.9 in 2019 to 5.6 ± 4.6 in 2020 ($p = 0.014$), but the prevalence rate for anxiety remained unchanged (19.8% vs. 18.7%, $p = 0.316$). The PHQ-9 score increased from 7.5 ± 5.7 in 2019 to 7.9 ± 5.6 in 2020 ($p < 0.001$), and the prevalence rate for depression increased accordingly (28.7% vs. 32.1%, $p = 0.002$).

**Conclusions:** The prevalence of depression amongst Norwegian high school students increased during the initial phase of the COVID-19 pandemic compared to pre-pandemic times, whereas prevalence rates for insomnia and anxiety remained unchanged. More longitudinal research is needed to increase our understanding of the effect of the COVID-19 pandemic and associated social restrictions on adolescent sleep and mental health.

**Disclosure**: Yes

**Conflict of Interest statement:** Part time employment by Wonderland AS.

## 25: SLEEP AND AGING

O085/P532 | **Objective sleep quality, its variability and cerebral *β*-amyloid burden in normal aging**

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**Introduction:** Alzheimer's disease (AD) is characterized by an accumulation of amyloid beta (A*β*) proteins in the brain and the causes of this accumulation need to be better understood in order to prevent it. There is some evidence indicating that slow wave sleep may constitute a critical period for A*β* brain extraction.

We assessed here the association between actigraphy-derived sleep quality and A*β* burden in the brain of cognitively normal elderly. Since the beginning of the night is rich in slow wave sleep, we specifically focused our analysis on the first part of the night.

**Methods:** This cross-sectional population-based study is a part of a protocol called EDUMA, including community dwelling elderly from the French region, Gironde. Participants were clinically assessed; underwent 9 days of actigraphy at home and had an A*β* Positron Emission Tomography scan with $^{18}$F-flutemetamol as well as a Magnetic Resonance Imaging scan. Sleep quality was assessed based on mean and intra-individual variability (standard deviation) of duration (min) and continuation (fragmentation index). Multiple linear regressions were used to determine the relationship between sleep parameters and brain A*β* burden in voxel-based analysis.

**Results:** A total of 86 subjects were included in the present analysis (80.3 ± 5.4 years; 48.8% of women). High intra-individual variability of sleep fragmentation was associated with a higher brain A*β* burden in the frontal cortex, the parietal cortex and the precuneus ($p < 0.001$, adjusted for age, sex, level of education and mean sleep fragmentation).

**Conclusions:** The intra-individual variability of sleep fragmentation in the first half of the night rather than its mean is associated with brain A*β* burden in cognitively normal elderly. This study highlights the relevance of the day-to-day irregularity of sleep continuation as a potential biomarker of early AD pathogenesis.

**Disclosure**: No

**Conflict of Interest statement:** Funded by France

## O182/P817 | Rest-activity rhythm fragmentation is associated with Locus coeruleus hypopigmentation: a retrospective post-mortem study

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**Introduction:** The brainstem locus coeruleus (LC) was recently put forward as a key nucleus to connect sleep-wake disruption and Alzheimer's disease (AD) pathophysiological processes. Here, we sought to investigate the relationships between post-mortem LC hypopigmentation, reflecting LC neurodegeneration, and retrospective rest-activity rhythm fragmentation metrics in a longitudinal dataset.

**Methods:** LC pigmentation ratings were extracted from autopsy data across 517 Rush Memory and Aging Project cases (mean age at death = 91.6 ± 6.2 y; 141 men, 376 women). For each individual, actigraphy-derived intradaily variability (IV), an objective measure of rest-activity rhythm fragmentation, was extracted at baseline (on average 6.3 y. before death) and at each subsequent year until death. In a subsample of 396 participants with at least two actigraphic time points, we used a linear mixed effect model to compute the slope of IV values across time. Logistic regressions models adjusted for age at death, sex and post-mortem interval were performed to assess whether baseline IV and its evolution over time could predict post-mortem LC pigmentation ratings. In the next step, additional models including AD-related variables of APOE genotype and cortical neuropathology (amyloid-beta and tau burden) were conducted to test for independence in the relationships between IV measures and LC pigmentation.

**Results:** Out of the 517 cases, 138 displayed LC hypopigmentation at autopsy. Higher baseline IV values were significantly associated with greater odds of LC hypopigmentation post-mortem (adjusted OR [95% CI] = 1.48 [1.22 – 1.79], $p < 0.0001$). Accordingly, a steeper increase in IV values across years significantly predicted LC hypopigmentation ratings (adjusted OR = 1.32 [1.05–1.65], $p = 0.02$). Crucially, these relationships remained significant independently of the effects of APOE and cortical AD neuropathology (baseline IV: adjusted OR = 1.52 [1.24–1.87], $p < 0.0001$; IV slope: adjusted OR = 1.34 [1.04–1.72], $p = 0.02$).

**Conclusions:** These findings highlight the importance of evaluating and monitoring rest-activity rhythm fragmentation to predict LC neurodegenerative processes in older populations, as far as 6.3 years before death and beyond the effects of APOE genotype and cortical AD neuropathology. Our results thus have implications for improved detection of at-risk individuals.

**Disclosure**: No

## O189/P818 | REM sleep is reduced in late middle-aged and older apoe4 allele carriers, independently of cognitive status, age, sex and sleep apnea

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**Introduction:** Sleep architecture is disrupted in patients with Alzheimer's disease (AD). Notably, REM sleep duration is reduced as of prodromal stages. Individuals carrying the ε4 allele of the *apolipoprotein E (ApoE4)* gene are at greater risk of developing mild cognitive impairment (MCI) and AD. An emerging literature suggests that *ApoE4* carriers with MCI may exhibit greater sleep alterations than non-carriers. We aimed at comparing sleep architecture between *ApoE4* carriers and non-carriers older individuals. Moreover, we tested the moderating impact of cognitive status, sex, age and obstructive sleep apnea on these associations.

**Methods:** We included 68 *ApoE4* non-carriers (66.5 ± 7.7 years old; 22% women; 64.7% cognitively normal and 35.3% with amnestic MCI) and 20 *ApoE4* carriers (66.8 ± 6.2 years old; 45% women; 60% cognitively normal and 40% with amnestic MCI), without dementia or other neurological or psychiatric disorders, and free of medication affecting sleep or cognition. They underwent in-laboratory polysomnography, *ApoE4* genotyping and a neuropsychological evaluation. Differences in sleep architecture between *ApoE4* carriers and non-carriers were assessed using ANCOVAs, controlling for age, sex, the apnea-hypopnea index and cognitive status (i.e., cognitively normal or amnestic MCI). Then, general linear models were conducted using the same variables to test interactions between *ApoE4* and potential moderating factors (i.e., cognitive status, age, sex, and apnea-hypopnea index, separately) on sleep variables.

**Results:** *ApoE4* carriers and non-carriers did not differ in terms of age, education, cognitive status ratio and sleep apnea-hypopnea index, but there were significantly more women in the *ApoE4* carriers' group (sex ratio: $\chi^2 = 4.1$, $p = 0.043$). Regarding sleep architecture, REM sleep duration and proportion were both reduced in *ApoE4* carriers (duration: $F = 9.4$, $p = 0.003$, $\eta^2 = 0.10$; proportion: $F = 9.5$, $p = 0.003$, $\eta^2 = 0.098$). Cognitive status, sex, age, or the apnea-hypopnea index did not significantly interact with *ApoE4* on these

associations. Other sleep variables were not associated with *ApoE4* genotype.

**Conclusions:** *ApoE4* carriers, who are at higher risk for AD, presented reduced REM sleep duration and proportion, independently of cognitive status, age, sex, and the presence of sleep apnea. These results support the notion that REM sleep alterations may reflect an increased AD risk, even before the onset of cognitive impairment.

**Disclosure**: No

## O191/P819 | Chronic napping alters cognitive performance in healthy older adults

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**Introduction:** The occurrence of napping increases with advancing age. Previous studies demonstrated that napping affect cognitive performance. However, whether this association depends on the cognitive domain and what are the underlying cerebral correlates remains to be explored. We assessed episodic memory, executive functions and attentional performance, as well as working memory, in healthy older adults with and without chronic napping habits.

**Methods:** Sixty-three individuals (69.2 ± 5.4 years, 22 women) were prospectively recruited with respect to their self-reported napping habits (no-nap ($n = 32$) and chronic nap ($n = 31$) group). Chronic napping was defined as a nap duration of at least 45 min per day, for at least 3 times a week, since at least one year. All participants completed a cognitive test battery, encompassing episodic memory, executive functions and attentional performance. A composite performance score was computed for each cognitive domain and *t*-tests were used to compare cognitive performance between groups. Participants also performed a Sternberg task in a 3T MRI scanner, during which working memory load was modulated through the number of items to be encoded (from 2 [low load] to 7 [high load]). Linear mixed-effect models were computed to assess whether task performance was related to working memory load between groups.

**Results:** Chronic nappers showed significantly worse performance in episodic memory ($t = 2.20$, $p < 0.05$) and executive functions ($t = 2.37$, $p < 0.05$) than no-nappers, but no significant difference was observed for attentional performance ($p = 0.59$). As expected, working memory performance at higher load (6 [$\beta = -0.038$, $p < 0.01$] and 7 items [$\beta = -0.096$, $p < 0.001$]) significantly decreased compared to the lowest load for the entire group. Interestingly, chronic nappers had lower performance ($\beta = -0.043$, $p < 0.05$) at the highest working memory load compared to no-nappers.

**Conclusion:** Our results go in line with previous findings by suggesting that chronic napping is associated with reduced executive functions, working memory, as well as episodic memory performance in healthy older adults. As napping is increasingly used as health indicator in ageing, a better understanding of the underlying mechanisms is relevant. Future analyses will explore differential recruitment of neuronal resources according to nap phenotype by using functional magnetic resonance imaging during the working memory paradigm.

**Disclosure**: Yes

**Conflict of Interest statement: Sources of funding:** Belgian Fund for Scientific Research (FNRS), European Research Council (ERC-Stg: COGNAP, ID:757763).

## O192/P820 | Sleep and circadian rhythmicity in healthy older adults at low and high genetic risk of alzheimer's disease: a multi-method research study

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**Introduction:** The risk of Alzheimer's Disease is increased in APOE-ϵ4 allele carriers and in those with sleep and circadian disturbances. However, the interrelationships between APOE-ϵ4 carriership, sleep and rest-activity patterns in healthy older adults are still unclear due to heterogeneity in published results. This can be related to methodological differences related to subjects' characteristics. There is also lack of experimental studies manipulating sleep to assess the interaction of the genotype with sleep-wake regulatory processes. We aimed to address this research gap.

**Methods:** One-hundred-sixty-one healthy participants have taken part in extensive screening sessions (51 APOE-ε4+, age = 63.18 +- 7.84; 110 APOE-ε4-, age = 65.66 ± 9.98) of which fifty-eight (28 APOE-ε4+, age = 64.45 ± 7.36; 30 APOE-ε4-, age = 65.23 +- 10.34) participated in a 14-days-long actigraphy session supplemented by sleep diary. Thirty-five individuals (18 APOE-ε4+, age = 64.21 ± 8.58; 17 APOE-ε4-, age = 65.00 ± 9.54) underwent a 2.5-days-long laboratory session in dim light condition (<10lx) and followed a modified constant routine protocol in the Sleep and Brain Research Unit(UEA). After a baseline night, participants were randomly assigned to either a 40-h sleep deprivation(SD) or a multi-nap (MN) experimental condition followed by a recovery night. Nine 80-min-long naps were scheduled every 4-h in the MN condition.

**Results:** ANCOVA controlled for age, and biological sex revealed no significant differences between APOE-ϵ4 allele carriers (APOE-ε4+) and non-carriers (APOE-ε4-) on Pittsburgh-Sleep-Questionnaire, Insomnia-Severity-Index, Epworth-Sleepiness-Scales and Munich-Chronotype-Questionnaire. Analysis of the actigraphy-based rest-activity patterns revealed no significant genotype effects except a decrease in Relative Amplitude(RA) in APOE-ϵ4 allele carriers compared to non-carriers ($p = 0.04$, $F = 4.58$, $\eta^2 = 0.07$; RA in APOE-ε4+:0.93 ± 0.03; RA in APOE-ε4-:0.95 ± 0.03). No significant

genotype differences were found in sleep macro-architecture during either baseline or recovery night and either experimental conditions (i.e., MN vs. SD), besides a trend toward a lower percentage of Total Sleep Time (TST) in N2 during baseline night in APOE-ε4+.

**Conclusions:** Our results suggest that APOE-ε4 carriership in healthy elderly adults has a limited impact on subjective and objective sleep quality and daytime sleepiness measures with evidence for a decrease in circadian rest-activity amplitude and a marginal decrease in the percentage of TST in N2. Further in-depth analyses are required to clarify whether differences may be still present in sleep microstructure, for example, microarousals and sleep-dependent oscillatory brain activity.

**Disclosure**: No

## 26: SLEEP AND GENDER

### O021/P225 | The influence of biological sex and age on spindle density in chronic insomnia

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**Objectives/Introduction:** Sleep architecture and brain oscillations have been shown to fluctuate across the lifespan. In particular, spindle density (SD) decreases in seniors compared to young adults. While female healthy sleepers have been shown to exhibit higher SD compared to males, research is limited on how biological sex influences SD in individuals with insomnia across the lifespan.

**Methods:** We studied 79 adults with chronic insomnia ($M = 21$; $F = 58$; Age: 49.06 ± 15.79). Whole night PSG recordings included 24 scalp-EEG sampled at 512 Hz, EOG, EMG (Somnomedics, Germany) and were scored according to the AASM guidelines. We detected spindles on central channels (Fz, Cz, Pz) using automatic detection. A multiple regression analysis was conducted to test for sex differences in SD across the lifespan. A univariate general linear model tested the interaction between sex and age on SD.

**Results:** Age did not differ between males and females ($p = 0.151$). After controlling for Age, males with insomnia spent more time in NREM2 [$F(2, 76) = 3.80$, $r = 0.30$, $p = 0.027$] and less time in NREM3 [$F(2, 76) = 11.19$, $r = 0.48$, $p < 0.001$], compared to females with insomnia. Females did not differ from males on SD [$F(1, 76) = 1.16$, $r = 0.47$, $p = 0.072$]. In Cz, there was a negative effect of Age on SD [$F(1, 77) = 18.11$, $r = -0.44$, $p < 0.001$] in both sexes ($M$: $r = -0.550$, $p = 0.01$, $F$: $r = -0.363$, $p = 0.005$). An interaction emerged between Age and Sex [$F(1, 75) = 1.27$, $p = 0.026$, $h^2 = 0.02$] with a steeper decline in SD across the lifespan for males than females. Age and Sex explained 22.5% of the variability in SD during NREM [$F(2, 76) = 11.00$, $r = 0.47$, $p < 0.001$]. Similar results were found for Fz, Pz, NREM2 and NREM3 alone (all $p < 0.05$).

**Conclusion:** These findings indicate that biological sex and age affect SD in those with chronic insomnia. Future studies should compare these findings to healthy sleepers and parse out group and sex effects in SD.

**Disclosure**: No

### O105/P533 | Sleep and sleep disorders during pregnancy and postpartum: the life-on cohort study

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**Objective/Introduction:** sleep disorders are frequent during pregnancy and puerperium and contribute to the development of several complications. However, objective polysomnographic (PSG) studies and longitudinal sleep assessments are few and often limited in scope. We aimed to prospectively assess sleep and sleep disorders during pregnancy and postpartum in a large cohort of women.

**Methods:** The life-ON is a multicenter, prospective study, recruiting consecutive pregnant women from the local hospital gynecological departments. Women receined a home polysomnography between the 23rd and 25th week of pregnancy and sleep-related questionnaires at 11 points in time during pregnancy and one year postpartum. Women between 18 and 55 years of age and without major morbidities, were recruited at a gestational age between 10 and 15 weeks. Frequency and course of daytime sleepiness, insomnia, low quality of sleep, restless legs syndrome, sleep breathing and periodic limb movements (PLMS) across pregnancy and puerperium were assessed.

**Results:** 439 pregnant women (mean age 33.7 ± 4.2 y) were enrolled, with full-night PSG data available for 353 women. Poor quality of sleep was reported by 34% of women in the first trimester of pregnancy, by 46% of women in the third trimester, and by as many as 71% of women in the first month after delivery. A similar trend was seen for insomnia. Excessive daytime sleepiness peaked in the first trimester (30% of women), and decreased in the third trimester, to 22% of women. Prevalence of RLS during pregnancy was 27%, with a peak

in the third trimester. Sleep-disordered breathing had a prevalence of 4.2% and correlated positively with BMI. A PLMS index larger than 4 was found in 55% of women. PSG data revealed that 24% of women slept less than 6 h, and 30.6% of women had a sleep efficiency below 80%.

**Conclusions:** The Life-ON study provides the largest PSG dataset coupled with longitudinal subjective assessments of sleep quality in pregnant women to date. Sleep disorders are highly frequent and distributed differently during pregnancy and postpartum. Routine assessment of sleep disturbances in the perinatal period is necessary to improve early detection and clinical management.

**Disclosure**: No

## 28: HEALTHCARE SERVICES, RESEARCH AND EDUCATION

### O048/P941 | THE IMPACT OF SMARTPHONE USE AND SHORT-WAVELENGTH LIGHT DURING THE EVENING ON SLEEP, CIRCADIAN RHYTHM AND COGNITIVE PERFORMANCE

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We here present our study investigating the effects of short-wavelength light from a smartphone during the evening on sleep and circadian rhythms. 33 healthy male adult subjects (mean age: 21.70 years, standard deviation: 1.91 years) participated in our within-subjects design where polysomnography and body temperature were recorded throughout one adaptation and three experimental nights. The light conditions were counterbalanced across the three nights. Cortisol, melatonin and affectivity (PANAS scale) were assessed before and after sleep. Subjects had to perform a declarative word-pair-association task as well as a Go/Nogo task which was presented in total four times per night. Further they read for 90min on a standardized smartphone (Samsung Galaxy A50) with or without a filter or from a book before going to bed during the experimental nights. Our results indicate reduced slow-wave-sleep and slow-wave-activity in the first night quarter after reading on the smartphone without a filter. Additionally a weaker cortisol-awakening-response was revealed after short-wavelength light exposure. Although subjective sleepiness (Karolinska Sleepiness Scale) was not affected, the evening melatonin increase was attenuated in both smartphone conditions. Accordingly, the distal-proximal skin temperature gradient increased less after short-wavelength light exposure than after reading a book. Interestingly, we could unravel that higher positive affectivity in the evening predicted better subjective but not objective sleep quality. Our results show disruptive consequences of short-wavelength light for sleep and circadian rhythmicity with a partially attenuating effect of blue-light filters. Furthermore, affective states influence subjective sleep quality and should be considered, whenever investigating sleep and circadian rhythms.

**Disclosure**: No

## LATE BREAKING ABSTRACTS

## 2: CELL AND MOLECULAR BIOLOGY AND GENETICS

### O073/P243 | Alpha power density in wake electroencephalography and its relationship to cerebral $A_1$ adenosine receptor availability in the human brain

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In human electroencephalography (EEG), alpha rhythm (8–13 Hz) is one of the most prominent features during rested wakefulness and it is a highly genetically influenced phenotype, which has been demonstrated in twin and test-retest studies. Its manifestation is related to cerebral energy metabolism and modulated by the level of attention and wakefulness.

Homeostatic and circadian effectors, which are known to impact the sleep-wake-cycle, can be considered when investigating brain oscillations like the alpha rhythm. Adenosine is a neuromodulator directly linked to energy metabolism through the breakdown of adenosine triphosphate (ATP) and acts as homeostatic sleep factor by activating adenosine receptors type $A_1$($A_1$AR) and $A_{2A}$($A_{2A}$AR), which are blocked by caffeine. Thus, adenosine and its receptors could have a modulatory effect on EEG parameters and alpha power density in particular.

In healthy human subjects, who were genotyped for a variant in the $A_{2A}$AR gene ADORA2A that influences caffeine sensitivity (single nucleotide polymorphism rs5751876), we quantified alpha power density with high density wake EEG and $A_1$AR availability using [$^{18}$F]CPFPX and positron emission tomography (PET) at rested conditions in a laboratory setting.

In homozygous C-allele carriers ($n$ = 27, 11 women), alpha power density levels were higher compared to heterozygous and homozygous carriers of the T-allele ($n$(C/T) = 23, $n$(T/T) = 5, 13 women) ($F_{(18,39)}$ = 2.29, $p$ = 0.015, Wilk's $\Lambda$ = 0.486; multivariate analysis

of variance [MANOVA]). A whole brain effect of ADORA2A genotype on $A_1$AR binding potential was found ($F_{(31,26)} = 2.84$, $p = 0.004$, Wilk's $\Lambda = 0.228$; MANOVA) and after correction for multiple testing, this effect was shown to be significant for the circumscribed occipital region of calcarine fissures. A correlation of individual alpha power density levels and $A_1$AR availability was not found.

Genetic variation in the adenosinergic system affects individual alpha power density, although a regional modulatory effect by $A_1$AR expression could not be demonstrated.

**Disclosure**: No

## 9: LEARNING, MEMORY AND COGNITION

### O066/P250 | Sleep-spindle clustering is relevant to the reactivation of the "trained" motor cortex and overnight gains in performance – evidence from a simultaneous EEG and fMRI study

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Ample evidence suggests that sleep facilitates the consolidation of newly learned motor skills. However, the neurophysiological correlates and neural mechanisms underlying the consolidation of such experiences during sleep are not yet fully understood. Research in our and other laboratories suggests that spontaneous reactivation of newly formed memory traces, hence facilitating their consolidation, is linked to sleep spindles occurring during non-REM sleep. However, there is no unitary view on whether all or only some spindles are associated with memory reactivation processes. Here we tested the hypothesis that, compared to sporadic spindles, spindles that occur in clusters are more crucial to sleep-dependent memory consolidation, and then sought to identify neural substrates associated with this clustering effect. To this end, we conducted a sleep study, recording brain activity using electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) simultaneously. Before sleep, participants ($n = 26$) were trained on a 5-element sequence of finger movements, using their left hand. To estimate overnight gains in performance – a measure of memory consolidation – participants were also retested 24 h post-training. Sleep spindles were detected automatically as brief bursts of activity (0.3–2 s) in the sigma (11–16 Hz) frequency range during non-REM sleep. They were then classified as clustered or isolated (i.e., less or more than 6 s apart, respectively). The results in 20 participants (mean age: 25.3 ± 3.5 years, 16 females), who met the inclusion criteria, revealed that the onset of longer spindle events (i.e., clusters that comprise more than 2 spindles versus isolated spindles) was associated with increased brain activity in key cortical and subcortical regions of the task-related network, including the sensorimotor cortices, striatum, and thalamus. Furthermore, when the analysis was limited to spindles detected over the motor cortex in the hemisphere contralateral to the trained hand, the pattern of increased activity for longer spindle clusters was strongly lateralized to this "trained" hemisphere, and participants with greater overnight gains in performance exhibited stronger activation of the "trained" primary motor cortex. These findings suggest that sleep spindles clustering facilitates reprocessing and consolidation of newly encoded motor memories involving brain regions that were initially engaged in the learning process.

**Disclosure**: No

### O074/P251 | Unique roles for REM sleep and slow wave sleep in the sleep-dependent evolution of brain circuits supporting spatial navigational memory

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**Introduction:** REM sleep and slow wave sleep (SWS) have both been implicated in offline memory processing, but their differences in oscillatory frequencies and neurotransmitter tone suggest potentially unique contributions.

**Methods:** 16 healthy subjects (31 ± 6 y., 9 female) completed spatial navigational encoding and recall using a virtual 3D Maze during two fMRI sessions (~7 p.m. and 8 a.m.) separated by 3 counterbalanced nights of polysomnography: undisrupted control, REM disruption, and SWS disruption, using auditory tones during real-time EEG monitoring. Each fMRI session consisted of six runs: three maze trials interleaved with three control trials. During maze trials, participants were instructed to reach a prespecified goal as quickly as possible, whereas during duration-matched control trials, participants navigated a *Z*-shaped corridor. Parameter estimates of the % change in blood-oxygen-level-dependent (BOLD) signal using the contrast maze-control were used as the primary metric. Regions of interest included the bilateral hippocampus, Para hippocampal gyrus, and amygdala.

**Results:** REM or SWS disruption with auditory tones resulted in significantly decreased time spent, reduced bout length, and increased arousal index of that stage. During the undisrupted control condition, we observed a significant reduction in activation of the bilateral hippocampus and Para hippocampal gyrus across sleep (evening-morning % change $= -0.26 \pm 0.11$, $p < 0.05$) and a significant increase in amygdala activation (evening-morning % change $= 0.51 \pm 0.17$, $p < 0.01$). During SWS disruption, we continued to observe a significant overnight decrease in hippocampal activation, but we failed to observed amygdala activation. In contrast, during REM disruption, hippocampal activation actually increased overnight, and we also observed increased amygdala activation. While we did not observe significant differences in overnight performance improvement

between conditions, greater evening hippocampal activity was associated with greater overnight change in maze completion times across sleep only during the undisrupted control condition (rho = 0.52, $p = 0.04$), but not during the REM or SWS disruption conditions.

**Conclusion:** Uninterrupted sleep supports redistribution of neural activity supporting spatial navigation, with significant decreases in hippocampal activity and increases in amygdala activity, potentially consistent with the systems consolidation hypothesis. REM disruption results in a failure of the hippocampus to decrease its navigation-specific activity overnight whereas SWS disruption results in failure to recruit amygdala activity overnight.

**Disclosure**: No

## 13: COMPUTATION/MODELLING

### O069/P257 | Capturing uncertainty in overnight sleep statistics using automatic scoring

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**Objectives:** Sleep staging is a crucial but labour-intensive diagnostic tool, compelling the use of automated machine learning models. These models are trained on scorings made by humans, which have imperfect agreement, resulting in uncertainty about the correct scoring. Recent developments in automatic sleep staging, such as hypnodensity, try to capture this uncertainty on an epoch-by-epoch basis. However, these methods inadequately capture the uncertainty of overnight sleep statistics. Here, we propose U-Flow, which given a single input PSG, outputs a desired number of plausible hypnograms, mimicking the diversity seen in human scorings.

**Methods:** The model was trained with 529 recordings of the Stanford Sleep Cohort (SSC; single scorer), all 80 recordings of the Dreem Open Datasets (5 scorers), and all 110 recordings of the Institute of Systems and Robotics dataset (2 scorers). The validation set consisted of the remaining 132 recordings of SSC (single scorer). The hold-out test set comprised 70 recordings of the Inter-Scorer Reliability Cohort (6 scorers).

We compared U-Flow to a hypnodensity-based U-Net model of similar computational complexity. For each input PSG, both models output 100 hypnograms, which were compared to those of the 6 experts. Accuracy and kappa were calculated through majority voting. Nine commonly-used summarizing sleep statistics were calculated from each hypnogram, including total sleep time, time spent in each stage, sleep onset latency, REM onset latency, and number of awakenings. Each sleep statistic for each recording was modelled as a normal distribution, resulting in a mean and a variance, where the latter expresses the uncertainty. The distance between the distributions of the experts and the model predictions was evaluated using the Kullback–Leibler divergence. Significance was tested through ANOVA.

**Results:** U-Flow was found to better predict the distribution of overnight sleep statistics by a human panel for 8 out of 9 parameters ($p < 0.05$), while not sacrificing accuracy and kappa. These were, respectively, 80.5% and 0.71 for U-Net compared to 82.4% and 0.73 for U-Flow.

**Conclusions:** U-Flow outperforms a hypnodensity-based U-Net model of similar computational complexity, in its ability to capture the uncertainty of overnight sleep statistics, as well as accuracy and kappa.

**Disclosure**: Yes

**Conflict of Interest statement:** At the time of writing, HG, RS, and PF were employed and/or affiliated with Royal Philips, a commercial company and manufacturer of consumer and medical electronic devices, commercializing products in the area of sleep diagnostics and sleep therapy. Philips had no role in the study design, decision to publish, or preparation of the abstract. SO received an unrestricted research grant from UCB Pharma and participated in advisory boards for UCB Pharma, Jazz Pharmaceuticals, Takeda, and Bioprojet, all paid to institution and all unrelated to the present work.

## 14: SLEEP DISORDERS - BREATHING

### O072/P258 | A novel classification of obstructive sleep apnoea enabling precision medicine to improve adherence to continuous positive airway pressure: a growth mixture modelling analysis

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**Introduction:** High non-adherence rates to CPAP remain a major obstacle to good outcomes in OSA. In trials, 29%–83% of patients do not adhere to CPAP. CPAP adherence in clinical practice, and the effect of clinical pathways and interventions, remain unknown because of incomplete datasets and use of non-clinically relevant criteria for adherence in previous studies. Patients are reported to become adherent or non-adherent to CPAP from treatment onset, forming the basis of current clinical practice, but the studies have been small. We addressed these evidence gaps using a large, UK multicentre clinical dataset, using changes to sleep centres' treatment pathways during the COVID-19 pandemic as a natural experiment.

**Methods:** Five sleep centres that telemonitored patient data in 2019 and 2020 were recruited. Using a 18% difference in CPAP adherence between years (Philips Respironics data), 80% power, $\alpha < 0.05$, $n = 92$ was required. Objective CPAP-usage data over the first three months of treatment was collected from 100 patients who started CPAP pre-pandemic (April 2019) and 100 patients post-start of pandemic (September 2020), per centre. CPAP adherence criteria: mean CPAP use ≥4 h/night for ≥70% of nights (for Night 1–3 period, median CPAP use used, as data non-normally distributed). Growth mixture modelling (GMM) and logistic regression were performed using all centres' data (1000 patients).

**Results:** Three months after treatment started, only 34% of patients were treatment-adherent in 2019 and 42% in 2020 ($p = 0.24$). GMM identified six distinct, CPAP-usage behaviours over the first month, each with a different likelihood of CPAP non-adherence at three months. Four behaviours consisted of changing (increasing or decreasing) CPAP use (54% of patients), two behaviours consisted of consistent "good" or "no" use (remaining 46%). Treatment pathway determined prevalence of behaviours and CPAP adherence at three months; OSA severity was a weaker determinant of CPAP adherence at three months.

**Conclusions:** CPAP use at treatment onset does not predict long-term adherence in most patients. This can explain why current practice is ineffective, and may even be detrimental, as the "changing users" are inappropriately managed as "consistent users". Our data supports precision medicine tailored to specific behaviour from Week 2 of treatment.

**Disclosure**: No

## 16: SLEEP DISORDERS - INSOMNIA

### O067/P263 | On the relationship between EEG spectral analysis and pre-sleep cognitive arousal in insomnia disorder – towards an integrated model of cognitive and cortical arousal

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**Objectives/Introduction:** According to the hyperarousal model, insomnia is characterized by increased arousal in the cortical, cognitive and physiological domains. However, the interaction between these arousal domains is poorly understood. The current study aimed to investigate cortical arousal during the night, pre-sleep cognitive arousal and the relationship between these two domains.

**Methods:** 109 patients with insomnia disorder (ID) and 109 age-and gender matched healthy controls were investigated on two sleep laboratory nights. EEG spectral power during NREM and REM sleep was analyzed as a measure of cortical arousal. In addition, patients completed the Pre-Sleep Arousal Scale (PSAS), which consists of two subscales, one for cognitive arousal (PSAS-CA) and one for self-reported somatic arousal (PSAS-SA). The relationship between the subscale scores and EEG spectral power was calculated by multivariate and univariate analyses of variance.

**Results:** During NREM and REM sleep, patients with ID ($n = 109$) compared to healthy controls ($n = 109$) showed significantly increased spectral power in the EEG gamma band, $F(1,216) = 13.58$, $p < 0.001$. In addition, patients with ID had significantly higher PSAS-SA scores than GSC (ID: $M = 12.4$, $SD = 4.4$; GSC: $M = 10.7$, $SD = 3.3$; $t(216) = 3.34$, $p = 0.001$) with a medium effect size ($d = 0.45$), and ID patients also had significantly higher PSAS-CA scores than GSC (ID: $M = 18.3$, $SD = 7.2$; GSC: $M = 10.6$, $SD = 2.9$; $t(216) = 10.33$, $p < 0.001$) with a large effect size ($d = 1.40$). The PSAS-CA score was significantly associated with increased NREM ($p = 0.001$) and REM gamma power ($p = 0.004$), whereas PSAS-SA was associated with significant decreases in NREM ($p < 0.001$) and REM gamma power ($p = 0.001$).

**Conclusion:** Consistent with our hypothesis, patients with ID showed increased cortical and cognitive arousal. Moreover, there was an association between these two arousal domains, which may indicate that cortical arousal during the night is (at least in part) elicited by pre-sleep worry and rumination.

**Disclosure**: No

## 17: SLEEP DISORDERS - PARASOMNIAS

### O068/P268 | Neuropathological alterations in subjects initially diagnosed by polysomnography with isolated REM sleep behavior disorder

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**Background**: REM sleep behavior disorder is a parasomnia caused by the dysfunction of the subcoeruleus nuclei and the n. magnocellularis and related circuits. More than 90% of isolated REM behavior disorder (IRBD) patients at 15 years of diagnosis are at risk of developing Parkinson's disease (PD, 45%), dementia with Lewy bodies (DLB, 45%) or multiple system atrophy (MSA, 10%). Neuropathological studies of firstly diagnosed IRBD are scarce.

**Methods:** Eighteen patients with IRBD diagnosed by polysomnography were followed up until death and participated in the Brain Donation Program (2005-2020). Standard neuropathological evaluation and semi quantitative assessment of pathological alpha-synuclein (AS) deposits and the degree of gliosis and neuronal loss in specific

brain areas, including those related to REM sleep behavior disorder, were performed.

**Results:** 94% of participants were male, with a mean age (+/− SD) of 71 ± 6 years at IRBD diagnostic PSG and of 80 ± 6 years at death. Clinical antemortem diagnosis was DLB ($n = 10$), PD ($n = 5$) and IRBD ($n = 3$). All patients had an underlying synucleinopathy, 17 of the Lewy body type (LBD) and one patient had a MSA. All had frequent brainstem alpha-synuclein pathology and 94% had moderate neuronal loss in the locus coeruleus/subcoeruleus complex. A caudo-rostral gradient of alpha-synuclein pathology from midbrain over limbic and neocortical areas was observed in IRBD patients that progressed to PD or DLB. All patients had some degree of co-pathology: 12 Alzheimer's disease neuropathological change (ADNC), of which 6 had intermediate/high severity (all in neocortical AS stages), 11 age-related tau astrogliopathy, 4 argyrophilic grain disease, 3 progressive supranuclear palsy and 3 limbic predominant age-related TDP-43 encephalopathy.

**Conclusions**: IRBD results from an underlying synucleinopathy with prominent brainstem involvement that may progress to DLB, PD or MSA. The gradient of pathology and neuroanatomical distribution is more in line with a "body-first" progression hypothesis of LBD. Among age-related co-pathologies, ADNC is particularly frequent in the neocortical LBD stages and likely modulates the clinical phenotype, especially dementia.

**Disclosure**: No

## 20: NEUROLOGICAL DISORDERS AND SLEEP

### O070/P273 | The role of locus coeruleus degeneration in sleep-wake and behavioral symptoms in early and late-onset Alzheimer's disease

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**Introduction:** Early-onset Alzheimer's Disease presentations (EOAD, under 65) frequently present with atypical phenotypes and a more aggressive disease course with a higher burden of neuropsychiatric symptoms than late-onset AD (LOAD). Current treatments for sleep and behavioral disturbances are still non-specific, causing side effects (sedation, falls). Identifying the underlying changes driving behavioral differences between EOAD and LOAD is crucial to developing tailored treatment avenues. The noradrenergiclocus coeruleus (LC), one of the first sites of tau deposition in AD, has been implicated in sleep-wake patterns and mood regulation. We aim to test the hypothesis that the LC is more affected in EOAD than LOAD by comparing LC volume (neuromelanin-sensitive MRI), noradrenergic activity (CSF noradrenaline -NA) and sleep-behavioral symptoms in biomarker-confirmed EOAD and LOAD cohorts.

**Methods:** Fifty-four subjects with AD biomarker-based diagnosis (20 EOAD, 34 LOAD) were recruited at the Hospital Clínic de Barcelona. All participants and informants completed the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Neuropsychiatric Inventory (NPI) questionnaires to assess the severity of sleep-wake and neuropsychiatric symptoms. In addition, they underwent a 3Tfast spin-echoMRI to measure LC volume and measurement of CSF NA. We compared LC volume, CSF NA, ESS, PSQI, and NPI between EOAD and LOAD. Linear regression models controlling by cognitive status (MMSE) were performed.

**Results:** EOAD compared to LOAD, showed higher NPI scores (NPI 21.6 ± 8 vs. 14.6 ± 8, caregiver distress 9.4 ± 3 vs. 4.7 ± 3, $p < 0.05$) and trended towards higher scores for ESS (7.4 ± 1 vs. 5.1 ± 1, $p = 0.05$) and PSQI (7.3 ± 2 vs. 5.6 ± 1, $p = 0.06$). EOAD showed lower LC volume (24.2 ± 2 mm3 vs 31.2 ± 1 mm3, $p < 0.01$) and CSF NA levels (117.7+12 pg/ml vs 179.7 ± 12 pg/ml) than LOAD. EOAD diagnosis was the main contributor to lower LC volume and CSF NA ($p < 0.01$) in regression models. NPI and ESS scores correlated with LC volume and CSF NA, respectively ($p < 0.01$).

**Conclusions:** The current preliminary study suggests that LC degeneration is greater in EOAD than LOAD. This difference may explain the EOAD-associated worse sleep-wake dysfunction and neuropsychiatric symptoms. Deep phenotyping/comparison of EOAD and LOAD can inform tailored treatment strategies for these behavioral symptoms.

**Disclosure**: No

## 25: SLEEP AND AGING

### O071/P285 | Obstructive sleep apnea is associated with telomere shortening: a population-based longitudinal study

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**Objectives/Introduction:** Evidence has shown that as the chronological age of an organism increases, there is a decrease in the telomere length via oxidative stress and inflammation pathways. Epidemiological studies have measured this parameter as the mean leukocyte telomere length (LTL) and several associations between LTL and age-related diseases have been described. Since the major pathophysiological factors related to obstructive sleep apnea (OSA) contribute to the exacerbation of inflammation and oxidative stress, the association of OSA and short telomeres has been proposed in many cross-sectional studies. Thus, the aim of this study was to evaluate the association between OSA and its associated factors with LTL in a population-based longitudinal framework.

**Methods:** We used data derived from the São Paulo Epidemiologic Sleep Study cohort, which was followed over 8 years. All individuals underwent polysomnography and had their blood collected for DNA extraction. OSA was defined according to AHI≥ 15 events/h and leukocyte telomere length (LTL) was measured through qPCR. The Generalized Estimating Equations (GEE) test was applied for the comparison

between baseline and follow-up, choosing the best model according to the lowest value of Quasi Information Criterion and considering age, sex and BMI as covariables; and Spearman correlations were applied to compare the delta values between baseline and follow-up.

**Results:** Of the 1,042 individuals in the EPISONO cohort, 68.3% accepted to participate in the follow-up study ($n = 712$). The 8-year telomere attrition was inversely associated with baseline OSA ($B = -0.026$, 95%CI $= -0.049$ to $-0.003$, $p = 0.028$). We observed negative correlations between delta LTL and the following delta variables: apnea-hypopnea index (rho $= -0.237$, $p \leq 0.001$), desaturation index (rho $= -0.300$, $p \leq 0.001$) and wake after sleep onset (rho $= -0.165$, $p \leq 0.001$). Also, delta LTL was positively correlated with deltas basal (rho $= 0.261$, $p \leq 0.001$), minimum (rho $= 0.283$, $p \leq 0.001$), and maximum (rho $= 0.268$, $p \leq 0.001$) oxygen saturation.

**Conclusions:** We could conclude that individuals with OSA had greater LTL attrition over the 8 years. Using a longitudinal approach, these findings confirm previous cross-sectional evidence that OSA is associated with accelerated biological aging. This work was supported by grants from AFIP, FAPESP, and CAPES.

**Disclosure**: No

## SYMPOSIA ABSTRACTS

### O139/P914 | All-optical dissection of thalamic control of cortical dynamics during sleep

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Brain activity during sleep is characterized by circuit-specific oscillations, including slow waves, spindles and theta, that are nested in thalamocortical or hippocampus networks. A major challenge is to determine the neural mechanisms underlying these oscillations and their functional implications. In this lecture, I will summarize our most recent studies investigating the role of the thalamus in the temporal and spatial organization of low frequency oscillations including slow waves, as well as their functional implication in sleep structure and functions.

**Disclosure**: No

### O228/P915 | Exploration of the effect of sleep parameters on gait

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**Introduction:** The relationship between sleep and postural control, which is the ability to control the body in space for balance and orientation, has long been studied across the life span and in different contexts. Sleep and gait, a sub-domain of postural control, are two essential, modifiable and age-sensitive functions, and deficiencies in each are considered hallmarks of the aging process. Abnormalities of gait are common among 75% of people over 70 years old, and are associated with loss of independence, morbidity and mortality. Significantly, recent studies demonstrate comorbidity between gait and sleep. Indeed, older adults with sleep complaints are at a four-fold risk of falls compared with those without these complaints. Since one of the primary goals of geriatric medicine is to identify populations at a higher risk for falls and functional decline as early as possible, exploring the interlink between gait and sleep is of top priority.

**Objective:** To explore the relationships between gait and sleep and the mechanisms underlying this link.

**Methods**: The talk will address a set of studies that have been conducted in our laboratory and systematically demonstrate the effect of sleep on gait, as well as identify the mechanisms underlying this relationship. More specifically, we will address the relationship between sleep and gait among community-dwelling older adults, including those with and without insomnia.

**Findings and conclusions:** We will describe the contribution of cognitive capacity and physiological mechanisms, including their effect among different age groups. The talk will identify major gaps in the current research and propose future directions for study.

**Disclosure**: No

### O115/P916 | Paradoxical somato-dendritic decoupling supports cortical plasticity during rem sleep

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**Introduction:** REM sleep is associated with the consolidation of emotional memories encoded by neuronal circuits from the limbic system and prefrontal cortex in mammals. Yet, the underlying neocortical circuits and synaptic mechanisms remain unclear.

**Objectives and Aims:** How prefrontal regions perform during REM sleep?

How do they store emotional memories during REM sleep?

**Results and Methods:** Here, we found that REM sleep is associated with a somato-dendritic decoupling in pyramidal neurons of the prefrontal cortex, using simultaneous 2-photon calcium imaging and electrophysiological recordings in sleeping mice. This decoupling reflects a shift of inhibitory balance between PV neurons-mediated somatic inhibition and VIP-mediated dendritic disinhibition, mostly driven by neurons from the central medial thalamus. We further showed that REM-specific optogenetic suppression of dendritic activity led to a loss of danger versus safety discrimination during associative learning and a lack of synaptic plasticity, whereas optogenetic release of somatic inhibition resulted in enhanced discrimination and synaptic potentiation.

**Conclusions:** Collectively, our results demonstrated that somato-dendritic decoupling during REM sleep promotes opposite synaptic plasticity mechanisms that optimize emotional response to future behavioral stressors.

**Disclosure**: No

## O193/P917 | 34 Dental-medical collaborative models and opportunities for the diagnosis and treatment of patients with obstructive sleep apnea cpap, mandibular advancement splints or both.

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Disease-specific therapies for OSA are Continuous Positive Airway Pressure (CPAP) and Mandibular-Advancement-Splints (MAS). Understanding patient objective adherence, treatment efficacy and personal preferences can provide vital information to clinicians that will assist them in choosing the right treatment for their patients.

**Objective:** As a relatively new and emerging therapeutic option, the alternating use of CPAP and MAS to improve treatment adherence was explored. We evaluated the comparative effectiveness of CPAP, MAS and the combinations of both, and how it impacts on quality of life and blood pressure.

**Methods:** This multi-center, double-randomized, open-label, two-treatment, three-phase clinical trial that consists of a titration/adaptation phase, a cross-over phase and an observational phase.

**Results:** 60% of the participants chose to use both treatments interchangeably. Our findings show that the interchangeable use of treatments can have an added benefit of greater overall adherence to therapy and lead to a greater improvement in patient centered outcomes. This new emerging therapeutic option showed that for ESS, FOSQ-10 and CFQ scores, a combination of therapies resulted in a higher percentage of patients achieving normal scores.

**Conclusions:** The use of combination of therapies does positively impact long-term overall adherence to treatment, as compared to having access to a single treatment modality.

**Disclosure**: No

## O133/P918 | RBD and lucid dreams: a window on dreams

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Dreams reveal a fascinating world which reflects our cognition and emotions during sleep. They are however difficult to study, as dream reports, are often biased by amnesia and reconstruction.

REM sleep behavior disorder is a parasomnia that should be detected and treated because it announces a neurodegenerative disease and can be responsible for injuries. Notably, the behaviors during RBD correspond to the dream content. This isomorphism makes it a powerful instrument to openly observe dream scenarios. In this direction, we built a repertoire of all behaviors, gestures, words and facial expressions visible in the REM sleeper, in order to answer questions such as: do non-dreamers still dream, do eye movements follow dream gestures, does the dream scenario unfold at a normal speed, who is the sleeper talking to, does he/she keep semantics and gestures similar to the waking one? We then focused on the facial expression of the sleepers (smile, frown, painful expression): this allowed us to show that there are as many negative as positive expressions during REM sleep in these patients, that the emotions follow one another at a higher speed than in wakefulness and that the negative emotions are expressed before the positive ones during a REM sleep phase and are more associated with REMs bursts.

Lucid dreaming is the contraposed model of RBD: the lucid dreamer is indeed paralyzed in REM sleep but she is aware of dreaming and can report her experience live via various signals. After discovering that patients with narcolepsy were powerful lucid dreamers, these last ones helped us understand how to vary breathing in REM sleep according to dream content. We were able to establish two-way communication (the beginning of a dialogue) at a relatively high level and thus identified brief windows during which sleepers have access to external information and are able to process it. These two parasomnias constitute a novel access to the ongoing dream that complements and clarifies the data from the dream narrative alone.

**Disclosure**: No

## O239/P919 | Changes in cortical network structure index transitions between states of consciousness

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**Introduction:** Changes in the brain underlying transitions into and out of unconsciousness and altered states of consciousness are postulated to be conserved no matter whether they occur during anesthesia, sleep, the psychedelic experience, or other circumstances. However, identifying these common neural signatures has proven elusive.

**Methods:** We explored changes in the organization of human cortical networks during anesthesia and sleep using diffusion map embedding to elucidate a functional geometry of recorded cortical regions. This analysis maps cortical location into a Euclidean space in which proximity indicates functional similarity using a normalized connectivity ("diffusion") matrix, itself a rich source of information about the network. We applied this analysis to intracranial electroencephalographical (EEG) recordings in neurosurgical patients.

**Results:** During stages of reduced consciousness, diffusion matrices exhibited decreased effective dimensionality (a measure of network entropy), reflecting reduced complexity. Furthermore, functional brain regions exhibited tighter clustering in embedding space with greater distances between regions, corresponding to decreased differentiation and functional integration. These changes were not region-specific, suggesting global network reorganization.

**Conclusions:** These results strongly suggest common neural substrates for loss and recovery of consciousness during anesthesia and sleep, providing a systems-level mechanistic understanding within an intuitive geometric context. This unifying framework for understanding altered states of consciousness lays the foundation for evaluation of cortical state transitions in clinical settings. Of particular interest for this panel, applying this analysis to resting state data recorded using scalp EEG or fMRI during the

psychedelic experience could provide objective measures that can be related to neurophenomenology. Application to data recorded during sleep after versus before treatment with psychedelics could inform hypotheses of regarding the pro-neuroplastic effects of these drugs.

**Disclosure**: Yes

**Conflict of Interest statement:** Paid consultant (incl. stock options) for VCENNA, Inc., a pharmaceutical startup working to bring psychedelics to market as treatments for psychiatric disorders.

## O131/P920 | State space analysis: Tracking trajectories of sleep stages in 2d space

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In both clinical and research context, sleep is generally categorized into discrete behavioral stages (NREM 1 through 3, REM, wakefulness) which are based on characteristic electroencephalogram (EEG), electromyogram and electrooculogram patterns. This traditional approach represents sleep architecture in a static way, but it cannot reflect variations in sleep across time. Furthermore, it leaves us with artificially defined behavioral states, some of them being heterogeneous or ill-defined. To overcome such static sequence of partially arbitrary behavioral states, other methods may be tested to offer new insights into sleep, its behavioral states and architecture. Here, we focus on state space analysis, a novel, frequency-based EEG analysis which has been introduced to investigate dynamic aspects of sleep. This previously established mathematical model of sleep EEG analysis considers dynamical aspects of sleep which are quantified by measuring the spectral variability of the sleep EEG (by means of state space velocity). Previous and current research has applied this method with different underlying mathematical models and in different populations (healthy people, different patient groups), and it offered new insights into sleep-wake characteristics in the healthy and the diseased brain. This lecture will not focus on the mathematical models, but on the outcomes and their potential impact on our understanding of sleep, its dynamics and regulation.

**Disclosure**: No

## O042/P921 | Obstructive sleep apneas are highly prevalent in a mouse model of down syndrome.

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Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing in developed countries and is associated with frequent arousals, sleep fragmentation, metabolic and neurocognitive impairments, arterial hypertension, increased risk of morbidity and mortality due to adverse cardiovascular events. Despite the well-recognized clinical relevance of OSAs, genetic studies of OSAs have lagged and better knowledge of OSA pathophysiology is needed for uncovering new treatments of both the ventilatory disorder and its multiple sequelae. Basic research on experimental animals allows to perform mechanistic studies and accelerate the development of new therapeutic approaches. Mice are the mammalian species of choice for functional genomics of integrative functions such as breathing during sleep. The use of mouse models in sleep apnea study is limited by the common belief that central sleep apnea (CSA) but not OSA may happen in rodents. This has led to intermittent hypoxia being used as a model of apnea in mice studies. The presence of OSA has recently been suggested in Bmp7 mice and in obese mice (leptin deficient mice, New Zealand mice), in which upper airway flow limitation with increases in inspiratory effort has been described. We developed an innovative protocol (combining electromyographic recording of diaphragmatic activity with monitoring of respiratory activity using whole body plethysmography) to investigate the presence of OSAs in a non-obese validated model (Ts65Dn) of Down syndrome (DS). DS, the most common human chromosomal disorder, is a complex condition entailing intellectual disabilities together with many other systemic dysfunctions, including OSAs. In DS patients, OSA prevalence is almost 100% in adults. We showed that Ts65Dn mice exhibit both CSAs and OSAs, and that they have a significantly higher occurrence rate of OSAs during REM sleep than control euploid mice. Ts65Dn mice could thus represent a promising candidate as a genetic mouse model of OSAs, to accelerate the understanding of the pathophysiology and genetics of breathing disorders during sleep.

**Disclosure**: No

## O119/P922 | Introduction to open science: Why and how it can be applied to sleep science

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Transparency and the efficient sharing of knowledge and information are fundamental elements of the scientific endeavour and the research enterprise. Nevertheless, and despite the integration of technological advancements, science today has not fully integrated these elements. Scholarly publications remain largely behind paywalls, while the sharing of data, methodologies, and analysis algorithms is not common practice. In the scientific ecosystem, open science refers to the unrestricted public availability of published articles, as well as the data, protocols, and analysis algorithms associated with each study. Open science does not come with a strict set of rules, but with a wide range of approaches, each aimed to alleviate at least one culprit of irreproducibility. The integration of open science approaches aims to

safeguard the credibility of published literature. It allows for scientific findings to be scrutinised, replicated, corroborated or contradicted, so new studies can be designed on a reliable evidence base.

Open science is not more imperative in sleep research compared to other disciplines. However, compared to other areas of social and biomedical sciences, we have to a lesser extent addressed this issue. This talk will be a primer to open science for sleep researchers. We will introduce culprits of irreproducibility, such as HARKing, p-hacking, undisclosed flexibility and small and underpowered studies, and discuss their relevance for our field. Finally, we will consider open science principles relevant to early and senior career researchers and present findings on our work regarding the current adoption of open science tools by sleep researchers.

**Disclosure**: Yes

**Conflict of Interest statement:** LB is a fellow of Reproducible Research Oxford, the local group of the UK Reproducibility Network. UKRN is an initiative aimed to promote open scholarship and research reproducibility across all disciplines.

## O197/P923 | Night Work, Sleep Duration and the Immune System

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**Introduction/Objectives:** Evidence suggests that night work, short sleep duration and sleep problems are associated with poor long-term health outcomes, including increased risk of infections. In this symposium, epidemiological data from recent studies among (a) patients in general practice in Norway and (b) day and shift/night workers participating in a large international study (ICOSS-2) on COVID-19 and long-covid, will be presented.

**Methods:** The study in general practice included a total of 1848 unselective patients visiting their general practitioner. The patients completed a one-page questionnaire while waiting for the consultation. The international study included a total of 7182 day and shift workers from 15 different countries around the world. These participants completed an online survey covering several aspects of sleep.

**Results:** The study from general practice showed that patients reporting a sleep duration of less than 6 h had significantly higher risk of infection (any type) compared to patients reporting 7–8 h of sleep (Relative Risk (RR) 1.27, confidence interval (CI) 1.11–1.46). Furthermore, the risk of infection was significantly higher in patients with chronic insomnia compared to patients without insomnia (RR 1.15, CI 1.05–1.27). Preliminary data from the ICOSS-2 show that the prevalence of COVID-19 was significantly higher among participants involved in irregular day work (20.7%) and shift/night work (25.3%) compared with participants involved in regular day work (18.9%). Furthermore, the prevalence of long-covid (according to WHO criteria) was significantly higher among irregular day workers (11.4%) and shift/night workers (13.6%) compared with regular day workers (8.4%).

**Conclusions:** These data indicate that shift/night work, short sleep duration and sleep problems are associated with an increased risk of infections, including COVID-19. Furthermore, preliminary data suggest that shift/night work also is associated with increased risk of developing long-covid. The possible mechanisms involved will be discussed.

**Disclosure**: No

## O058/P924 | Mathematical models of rem sleep regulatory networks

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**Introduction:** The ultradian alternation between rapid eye movement (REM) sleep and non-REM (NREM) sleep is thought to be produced by the state-dependent activity of "REM-on" and "REM-off" brainstem and hypothalamic neuronal populations that, respectively, promote or suppress REM sleep. Synaptic interactions among these populations define REM sleep regulatory networks. However, the identity of the neuronal populations and the mechanisms by which their interactions initiate, maintain, and terminate REM sleep are not fully known.

**Objectives:** We use physiologically-based mathematical models to explore the dynamic mechanisms associated with competing hypotheses for network-based REM sleep regulation.

**Methods:** We construct dynamic, mathematical models of networks of REM-on and REM-off neuronal populations based on hypotheses of reciprocal interaction (RI) or mutual inhibition (MI). We consider multiple targets and actions of short-term REM sleep homeostatic pressure on network populations. We analyze the mechanisms in these networks that generate regular alternation of activity which would result in NREM-REM ultradian rhythms. We systematically analyze the sensitivity of alternating behavior in the networks to compare the robustness of NREM-REM rhythms in each model network.

**Results:** In the RI network, NREM-REM alternation arose directly from network interactions while in MI networks a REM sleep homeostatic drive was necessary to induce NREM-REM alternations. Comparative analysis of MI networks revealed that NREM-REM alternations were produced more reliably when the REM homeostatic drive acted on the REM-off population, either to terminate or initiate REM episodes. Model analysis predicted that key elements of network structure may be inferred by experimentally activating the synaptic pathway from REM-on to REM-off populations and assessing the effects on REM sleep. Additionally, the hypothesized post-REM refractory period can be achieved in an MI network with a modulated short-term REM homeostatic drive.

**Conclusions:** Dynamic mathematical modeling connects specific network structures of REM-on and REM-off neuronal populations to the mechanisms and dynamics of NREM-REM ultradian alternation they

produce. Comparative analysis of different networks identifies key targets for future experimental work to distinguish the structure of the physiological REM sleep regulatory network.

**Disclosure**: No

## O049/P926 | The janus-face role of light prior sleep

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When prescribing light therapy to a patient, one should know, similar to a centrally acting drug, its active substance and its mode of action on specific receptors in the brain. The active agent "light" is determined by its spectrum, which differently activates five photoreceptors in the retina, which is part of the central nervous system. Light has an interesting Janus function, such that depending on the timing, light can induce a circadian phase advance or delay, and light can prevent or promote sleep in humans. Classical drugs do generally not have such characteristics when used in the recommended dosage. A blood pressure medication, for example, does not lower blood pressure or raise blood pressure depending on the timing of the drug. Therefore, light therapies and light solutions in the workplace are complex and highly dependent on the problem to be solved.

In a meta-analysis, we recently demonstrated that evening light before bedtime has an alerting effect and, in a dose-dependent manner (melanopsin-weighted brightness), prolongs sleep latency and shortens sleep duration. However, we could also show that warmer light colours in the evening and metamerically-weighted low melanopic light significantly reduce this negative effect on sleep. Thus, one can even speak of a sleep-promoting light application in the evening before bedtime.

Recent evidence shows that homeostatic sleep regulation is also affected by prior history of light exposure besides the circadian timing system. Our data indicate that both the duration and the intensity of illuminance levels modulate the relative increase in sleep delta activity after sleep loss in humans. Thus, working extended h under low illuminance may negatively impact subsequent sleep intensity.

Evidence-based recipes for light as a non-pharmacological agent to improve sleep, alertness, circadian melatonin rhythms, and well-being will be presented in the scope of newly developed LED sources implemented in luminaires and visual displays.

**Disclosure**: No

## O142/P927 | My sibling with down syndrome struggles with sleep- what does that mean for me?

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**Introduction:** Sleep disorders are highly prevalent in children with Down syndrome (DS). However, the impact of these problems on families is understudied and, the perspective of siblings has not been widely reported.

**Aims:** This study aims to understand the experiences of siblings of children with DS who have clinician-diagnosed sleep difficulties.

**Methods:** Semi-structured interviews were conducted with 10 siblings of children with DS. All the children with DS were receiving care from a tertiary sleep clinic for management of a sleep problem. Reflexive Thematic Analysis was operationalised for data analysis. Siblings were asked to consider how the sleep difficulties faced by their sibling with DS impacts on them. Specifically, they were asked about their sleep quality, mental health, quality of life and the impact on their day-to-day activities and family function.

**Results:** All siblings reported that their sleep was disrupted by having a sister or brother with DS and sleep problems. Older siblings described the impact on their sleep quality in more detail, expressing how they felt when tired and how they were disturbed through the night. The context of the family impacted how affected the siblings felt by the sleep problems in the child with DS. For example, whilst those who identified as having a strong, close bond to the child with DS were more likely to be disrupted at night, they were also reported being more satisfied with their family relationships and dynamics.

**Conclusion:** Valuable insights are provided from siblings of children with DS on how sleep problems impact on their families. Siblings who describe a loving relationship with the child with DS are more likely to normalise their own sleep disruption and the impacts on their lives. This study highlights the importance of providing care to the entire family when managing sleep problems in children with DS.

**Disclosure**: No

## O054/P928 | Insomnia and stress: Moving beyond diathesis stress

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**Introduction:** While the negative consequences of insomnia are well-documented, a strengths-based understanding of how sleep can promote health promotion is still emerging and much-needed. Correlational evidence has connected sleep and insomnia to resilience; however, this relationship has not yet been experimentally tested. This talk will examine resilience as an ingredient and outcome of insomnia treatment.

**Methods:** Participants were randomized to either digital Cognitive Behavioral Therapy for insomnia (dCBT-I; $n = 358$) or sleep education control ($n = 300$), and assessed at pre-treatment, post-treatment, and one-year follow-up. Change in self-reported resilience was tested across the time points, and also examined as a mechanism driving insomnia and depression as outcomes. A follow-up study during the COVID-19 pandemic further examined the protective effect of dCBT-I.

**Results:** dCBT-I resulted in greater improvements in resilience compared to the sleep education control. The improved resilience was a significant mediator of reduced insomnia and depression severity following treatment. Furthermore, improved resilience following dCBT-I also reduced insomnia and depression at one-year follow-up by lowering latent risk. Sensitivity analyses indicated that each point improvement in resilience following treatment reduced the odds of insomnia relapse and incident depression one year later by 76% and 65% respectively. Finally, those who previously received dCBT-I demonstrated greater resilience via protection from insomnia, depression, and COVID-19 specific stress.

**Conclusions:** Improved resilience is a contributing mechanism to treatment gains following dCBT-I and may further protect against longer-term insomnia and depression by reducing risk.

**Disclosure**: No

## O217/P929 | New technologies and approaches for studying sleep and cognition in dementia 4

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**Introduction:** Sleep is thought to contribute to brain function across the life span and disturbed sleep is a risk factor for, and a symptom of dementia. However, the nature and extent of the sleep disturbances and how they relate to cognition in dementia remain poorly characterised. Addressing these gaps in our knowledge requires novel approaches and technologies for longitudinal assessment of sleep and cognition at scale and in the community.

**Objectives:** The objectives of this symposium presentation are to:

1. Review results of a recently published study in which sleep and cognition were assessed longitudinally in people living with dementia and age matched controls. 2. Review results of a recently completed validation study of wearables and nearables (contactless devices) for the recording of sleep in a heterogenous population of older participants.

**Methods:** Study 1 (Balouch et al., Alzheimers Dement [Amst]. 2022 May 16; 14(1):e12303).: The association between night-to-night variation in sleep with day-to-day variation in vigilance, cognition, memory, and behavioural problems was investigated in 15 participants with mild Alzheimer's disease, eight participants with mild cognitive impairment (MCI), and 22 participants with no cognitive impairment (NCI) during a two week period. Associations between daytime measures and four principal components of sleep (duration, quality, continuity and latency) were quantified using mixed-model regression.

Study 2 (Unpublished): Sleep was assessed with a number of wearables and contactless/nearable devices in 35 older participants and compared to gold standard polysomnography.

**Results:** Study 1: Day-to-day variation in several aspects of daytime function associated significantly with night-to-night variation in sleep duration and continuity.

Study 2: Accuracy of sleep assessments varied across devices but some aspects of sleep were adequately quantified by some of the devices.

**Conclusions:** New technologies and approaches for studying sleep and cognition in dementia hold promise for better understanding of the contribution of sleep to cognitive decline.

**Disclosure**: No

## O240/P930 | The role of A1 adenosine receptors for trait characteristics in cognitive performance impairments after alcohol intake

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In the brain, adenosine and its receptors are involved in sleep-wake-regulation. Sleep loss can have tremendous impact on cognitive performance in some individuals whereas others seem resilient. The sedating effects of alcohol intake on cognitive performance show surprising similarities to that observed after sleep loss. The negative effects of both conditions sleep loss and alcohol intoxication, on cognitive performance can be antagonized by caffeine which unselectively blocks cerebral adenosine receptors. We show here that the individual susceptibility to the performance impairing effects of sleep loss and alcohol involve the adenosine system and share trait characteristics.

**Disclosure**: No

## O144/P931 | Neuropsychological findings in children with down syndrome with or without obstructive sleep apnoea

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**Introduction:** Obstructive sleep apnea (OSA) is highly prevalent among individuals with Down syndrome (DS). Untreated OSA in the general population is widely reported to be associated with difficulties in attention, memory, executive functioning, intellectual ability, language skills, externalizing and internalizing behavior challenges, and poor social functioning. Few have examined these

associations among individuals with DS, and the non-physiological consequences of OSA require examination to inform treatment planning.

**Aims:** This study aimed to investigate the association between OSA and aspects of cognition, language, behavioral, and social functioning in youth with DS aged 6–17 years old.

**Methods:** Participants were 111 youth with DS and their caregiver. Youth with DS were assessed on cognitive and language abilities (SB5, EVT3, PPVT5). Caregivers completed questionnaires (OMQ-PF, BRIEF2, CBCL, SRS2, CSHQ) and reported on their child's medical conditions, including OSA and use of oxygen or positive airway pressure (PAP). Children diagnosed with OSA yet who were either not receiving treatment or were not complying with prescribed PAP were categorized as "OSA symptoms" ($n = 30$). Children with no diagnosis of OSA ($n = 63$) and children diagnosed with OSA but reported to be using oxygen or PAP ($n = 18$) were categorized together as "no OSA symptoms" ($n = 81$).

**Results:** Multivariate Analysis of Variance (MANOVA) was used to compare two groups, participants with DS with and without OSA symptoms. Results revealed that participants with OSA symptoms show significantly lower scores in IQ ($F = 4.28$, $p = 0.04$) and experience more challenges with emotional regulation ($F = 5.32$, $p = 0.02$), everyday memory ($F = 4.75$, $p = 0.03$), attention ($F = 9.30$, $p < 0.01$), internalizing behavior ($F = 5.49$, $p = 0.02$), social behaviors ($F = 5.18$, $p = 0.02$), and behavioral sleep habits ($F = 5.24$, $p = 0.02$) than those without OSA symptoms.

**Conclusion:** Consistent with previous studies among typically developing children and individuals with DS, our results demonstrate that participants with DS with OSA symptoms experienced more challenges in cognition, attention, and daily memory. The study highlights the importance of OSA treatment in children and adolescents with DS.

**Disclosure**: No

## O138/P932 | Locus coeruleus times infraslow thalamocortical dynamics during nrem sleep

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The noradrenergic Locus Coeruleus (LC) system is commonly associated to stress and attention during wakefulness and its activity is highly dependent on behavioral states. During non-rapid-eye-movement (NREM) sleep the LC is also active, playing roles in sleep spindle activity (brief sinusoidal events within the 10–15 Hz range), sensory arousability and sleep-dependent memory consolidation. However, many elementary questions remain unknown: how much noradrenaline (NA) is released, where it acts during NREM sleep, and what are LC's roles for NREM sleep. We examined these questions *in vivo* using the newly developed NA biosensors $GRAB_{NE1h,1m}$ in combination with polysomnographic monitoring of natural sleep in mice (Osorio-Forero et al.,2021). We observed recurrent fluctuations of the levels of free NA in the primary somatosensory nucleus of the thalamus on an infraslow, ~50-s time-scale. Mean NA levels of these infraslow variations during NREM sleep were greater than the ones of quiet wakefulness, while they declined in REM sleep. Low NA levels during NREM sleep coincided with a clustering of sleep spindle rhythms in the forebrain and with low heart rate (~400 bpm). Conversely, NA levels were high when sleep spindles were scarce and when heart rate was high (~500 bpm). We addressed the origins of these fluctuations by using local intrathalamic pharmacology and closed-loop optogenetic LC manipulation timed to NREM sleep moments. Pharmacological blockade of noradrenergic signaling in thalamus suppressed sleep spindle clustering on the infraslow scale, but spindle properties remained intact. Using optogenetics, we could suppress, lock or entrain sleep spindle clustering or heart rate variations. Sleep spindle clustering required noradrenergic modulation of thalamic nuclei but not of cortical circuits. Whole-cell patch-clamp recordings *in vitro* showed that NA release from local LC fibers onto thalamic nuclei activated α1- or $\beta$-adrenergic receptors, to depolarize membrane potentials over the tens-of-seconds time scale. We conclude that noradrenergic signaling by LC divides NREM sleep into substates that differ in terms of central (spindles) and autonomic (heart rate) physiological correlates. As these correlates parallel varying sensory arousability from NREM sleep (Lecci et al.,2017; Cardis et al.,2021), we propose that LC signaling renders NREM sleep more "wake-like" on the close-to-minute-time scale.

**Disclosure**: No

## O225/P933 | A role for astroglial calcium in sleep homeostasis

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**Introduction:** Mammalian sleep expression and regulation have historically been thought to reflect the activity of neurons. Changes in other brain cells (glia) across the sleep-wake cycle and their role in sleep regulation are comparatively unexplored.

**Objectives:** To determine changes in activity in astrocytes across the sleep-wake cycle and in response to sleep deprivation and to determine more directly the role of astroglial calcium in sleep homeostasis.

**Aims:** Aim 1-descriibe activity changes in astrocytes using genetically encoded calcium indicators, 1 and 2 photon microscopy combined with polysomnography in non-anesthetized mice. Aim -2 determine the effects of conditional and selective depletion of astroglial calcium on sleep homeostasis.

**Methods:** Combination of 1-2 and 2 photon microscopy with mouse polysomnography and inducible CRE-mediated deletion of STIM1, a rate-limiting component of calcium metabolism in the ER.

**Results:** We show that sleep and wakefulness are accompanied by state-dependent changes in astroglial activity. Astroglial calcium signals are highest in wake and lowest in sleep and are most pronounced in astroglial processes. We also find that astroglial calcium signals

during non-rapid eye movement sleep change in proportion to sleep need. In contrast to neurons, astrocytes become less synchronized during non-rapid eye movement sleep after sleep deprivation at the network and single-cell level. Finally, we show that conditionally reducing intracellular calcium in astrocytes impairs the homeostatic response to sleep deprivation.

**Conclusions:** Astroglial calcium activity changes dynamically across vigilance states, is proportional to sleep need and is a component of the sleep homeostat.

**Disclosure**: No

## O060/P934 | From genome to sleep phenome and the omic dynamics in between

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Sleep is highly complex in its manifestation and regulation. Sleep also greatly varies among individuals of a given species, attributable, in large part, to genetic factors. We and many others have leveraged this genetic variability to address questions related to sleep regulation, sleep function, abnormal sleep, and the consequences of poor or insufficient sleep. Accordingly, numerous genotype-phenotype associations have been reported. Studies quantifying the transcriptome and, subsequently, other omics phenotypes under various experimental conditions, brought additional insights into the molecular substrates of sleep regulation. Moreover, the importance of the contribution of the accessibility of non-coding regulatory elements in explaining phenotypic variation, are increasingly acknowledged in sleep research. With a dynamic analysis of ATAC- and RNA-seq data we could show that chromatin state rapidly changes with sleep and wakefulness pointing to candidate 'pioneer' transcription factors targeting other transcription factors setting in motion a cascade of events leading to the profound changes in the brain transcriptome. While much has been learned from these separate efforts, studies combining these various data types are few. We performed a higher-order, system-level analyses integrating high-resolution genotype information with multi-tissue epigenome, transcriptome, metabolome, and sleep/wake phenome data obtained in a genetic reference population of mice. Such systems genetics approach allows to track the flow of information from DNA to phenotype and how environmental challenges such as sleep deprivation alter this information flow. Sleep deprivation extensively affected the "systems genetics landscape" at all levels with numerous genetic loci not only affecting the magnitude of the effect but also the direction of change. The study confirmed known pathways and revealed new pathways shaping recovery sleep and the EEG.

**Disclosure**: No

## O123/P935 | Systemic post-mortem evaluation of hypothalamic neuronal sleep-wake populations in narcolepsy type 1: an unexpected finding

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Narcolepsy type 1 (with cataplexy) is a rare invalidating chronic sleep disorder caused by a loss of the neuropeptide hypocretin (orexin), presumed to be due to an auto-immune process. Besides the hypocretin system, there may be other hypothalamic neurotransmitter systems involved in the sleep-wake symptoms of narcolepsy. We systematically quantified immunohistochemically stained sleep-wake related neuronal populations and the presence of microglia reactions in the hypothalamus using unbiased stereological methods comparing narcolepsy type 1 ($n = 5$) and matched controls ($n = 5$). Results**:** (1) Biological clock**:** there was no difference in the numbers of vasopressin (AVP)-expressing neurons in the suprachiasmatic nucleus (SCN). (2) Sleep promoting neurons: the density of galanin positive neurons in the ventrolateral preoptic nucleus (VLPO) was stable. (3) Arousal related neurons: we confirmed the hallmark loss of hypocretin-1 expressing neurons and the increased numbers of histidine decarboxylase (HDC) positive histaminergic neurons. The density of choline acetyltransferase positive neurons in the nucleus basalis of Meynert was unchanged. In addition, surprisingly, we found a selective and strong reduction in the number of corticotropin-releasing hormone (CRH)-positive neurons in the paraventricular nucleus of narcolepsy, but not of intermixed vasopressin, oxytocin, or tyrosine hydroxylase positive neurons. In line with it, significant less CRH-positive fibers were observed in the median eminence. Moreover, the densities of vasopressin and oxytocin in the supraoptic nucleus and neuropeptide Y and proopiomelanocortin immunoreactive neurons in the infundibular nucleus were all similar. (4) Microglial reactions: The presence of Ionized calcium binding adaptor molecule 1 (IBA-1) was significantly higher in the hypocretin area, but not in any other adjacent area such as in the paraventricular region or in the tuberomamillary region. The human leukocyte antigen (HLA)-staining was similar in all these areas. We found a significant and specific reduction in the number of CRH neurons in narcolepsy type 1. These neurons are known to be involved in sleep-wake regulation, but primarily have hypothalamic-pituitary functions. This surprising decrease in CRH neurons in narcolepsy may together with a low hypocretin level contribute to sleep-wake symptoms. It might provide novel targets for diagnostics and therapeutic interventions.

**Disclosure**: Yes

**Conflict of Interest statement:** RF received research support from Bioprojet en Jazz Pharma, and consultancy fees from Bioprojet and Takeda.

## O065/P936 | RLS, from mice to humans: towards an understanding of the whole picture

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Until recently, our understanding of the pathophysiology of RLS has been characterized by the presence of fragmented, sometimes incompatible pieces of evidence, and a poor heuristic understanding.
The present talk will attempt to integrate the major clinical and experimental neurobiological findings into a global pathogenetic model which also integrate also recent genetic findings indicating that RLS has aspects of a genetically moderated neurodevelopmental disorder involving mainly the cortico-striatal-thalamic-cortical circuits. Brain iron deficiency (BID) remains the key initial pathobiological factor and relates to alterations of iron acquisition by the brain, also moderated by genetic factors. Experimental evidence obtained in animal models indicates that BID leads to hyperdopaminergic and hyperglutamatergic states that determine the dysfunction of cortico-striatal-thalamic-cortical circuits in genetically vulnerable individuals. However, the enhanced arousal mechanisms critical to RLS are better explained by functional changes of the ascending arousal systems. Furthermore, experimental and clinical studies suggest that a BID-induced hypoadenosinergic state provide the link for a putative unified pathophysiological mechanism for sensorimotor signs of RLS and the enhanced arousal state. The model has received clinical validation by recent studies showing the efficacy of glutamatergic (perampanel, alpha-2 delta ligands) and adenosinergic (dipyridamole) drugs.
**Disclosure**: Yes
**Conflict of Interest statement:** Research Grants: Roche, MSD
Consulting: Roche, Idorsia.

## O195/P937 | Timing of sleep and meals in night shift workers

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**Introduction and objectives**: Night work leads to circadian disruption, which may provide a link to the development of diseases. In two quasi-experimental studies, we investigated the interplay between scheduling of night work, timing of sleep and meals and diurnal rhythms of cortisol and melatonin.
**Methods and results:** In the first study, the aim was to study nighttime eating and circadian disruption. 37 male police officers collected data on the last day in three schedules of two, four and seven consecutive night shifts. 16 officers (43.2%) reported eating at least one main meal between midnight and early morning in all three schedules. Changes in diurnal rhythms were assessed by cortisol and melatonin concentrations in saliva. The phase of diurnal cortisol rhythm was delayed with 2:10 h (95% CI 0:24-3:56 h) and the lowest cortisol concentration was 66% lower (95% CI 47–94%) for night eaters compared to non-night eaters. The association between nighttime eating and diurnal rhythms of cortisol did not differ with number of consecutive night shifts. There was no association between nighttime eating and diurnal rhythms of melatonin concentrations.
The second study aimed to compare the timing of sleep among 68 male police officers with night shift work and 100 participants with permanent night work. Preliminary results show, that 74% of night shift workers and 69% of permanent night workers fell asleep between 7:00 a.m. and 9:00 a.m. after a night shift. The same sleep patterns were only found among 0.5% of night shift workers and 1.5% of permanent night workers on a recovery day (day off or a day shift). 85% of shift workers and 68% of permanent night workers fell asleep between 10:00 p.m. and 2:00 a.m. on a recovery day, whereas 6% of night shift workers and 22% of permanent night shift workers fell asleep between 2:00 a.m. and 6:00 a.m.
**Conclusions:** Timing of meals during night shifts are related to changes in diurnal rhythms but it does not depend on the number of consecutive night shifts worked. The majority of night shift workers and permanent night workers sleep during the night on days off. The association between these acute changes and health remains to be established.
**Disclosure**: No

## O125/P938 | Influences of latitude, light and covid-19 on sleep and circadian status

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**Objectives:** The latest insights on the human circadian status and health from the field studies of population samples living at (sub-)Arctic latitudes in Russia are presented.
**Methods:** 1229 healthy subjects participated in three studies – one questionnaire-based, and two – physiological, utilizing circadian measurements in different seasons of the year.
**Results:** *Study* "*W-S time*". We investigated the winter-summer difference in circadian health in subjects living in Novosibirsk (55°N; $N = 46$; no daylight-saving time transitions), some got up earlier, at ~6 a.m., and some later, at ~7 a.m. We found a half-an-hour phase delay, greater phase variability, and distortion ($N = 8$) of the 24-h salivary melatonin rhythm in winter. This was accompanied by the higher post-awakening subjective sleepiness (indicating a greater need for sleep) and higher post-awakening salivary alpha-amylase

levels along with their blunted decline (indicating stress). The phase delay and alpha-amylase increase were attributable mainly to the 7 a.m. group. *Study* "*GCCS-Russia*". Within the Global Chrono Corona Survey (GCCS) in Tyumen district (57–66°N), age range 18–22 ($N = 1139$), we examined the link of the subjectively scored change in outdoor light exposure (OLE) and screen time (ST), caused by COVID-19 lockdown, with questionnaire-defined proxies of circadian health. OLE decrease, when accompanied by ST increase, was associated with significantly later mid-sleep time (defined by Munich Chronotype Questionnaire), deterioration of sleep, physical activity and quality of life. *Study* "*Light-Arctic*" *(ongoing)*. In the spring session of the "Light-Arctic" study (which is similar to the "W-S time" study), data from week-long actimetry of 44 volunteers living in Tyumen district (66°N) were analyzed. Absolute and normalized (to the mean) 24-h amplitude of blue light exposure was positively correlated with the amplitudes of wrist temperature and activity rhythms, respectively. Both correlations were significant only in a subgroup with normal body mass index, but not with BMI > 25. The amount of blue light at night hour correlated positively with morning cholesterol.

**Conclusion:** The studies show a poorer circadian health in winter and highlight the importance of circadian light hygiene for the wellbeing.

**Funding:** Russian Foundation for Humanitarian Research (grant No 15-36-01023), and West-Siberian Science and Education Center, Government of Tyumen District (Decree of 20.11.2020, No.928-rp).

**Disclosure**: No

## O137/P939 | Midline thalamic nuclei contribution to cortical slow oscillations synchronization.

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**Introduction:** Slow-wave sleep is characterized by near-synchronous alternation of active Up states and quiescent Down states in the neocortex. Coordinated Up states synchronize activity in relevant cortical areas and Down states are required to separate these periods of activity to avoid interference between information encoded in different Up states. Global Up states are generally initiated in the frontal areas and then propagate to more posterior regions, while Down state transition appears to be more synchronous across cortical areas. The cortex itself can maintain Up and Down state alternation, however the full expression of these oscillations requires intact thalamocortical circuits. Sensory thalamic neurons can drive Down to Up transition, but the mechanisms allowing for synchronized Down state transition remain to be uncovered.

**Objectives:** Here we hypothesize that Down state transition is an active global process and is driven by subcortical inputs. Higher-order thalamic nuclei, in particular from the midline thalamic nuclei (MTN), project broadly across the neocortex and are therefore good candidates. We propose that MTN, via their projection to neocortical layer 1 neurogliaform interneurons, promote sleep oscillation coordination coordination.

**Methods:** We combine local field potential, single-unit, and patch-clamp recordings in conjunction with optogenetic stimulation and silencing in mice in vivo.

**Results:** We show that midline thalamic neurons terminate Up states synchronously across cortical areas. Burst activity in midline thalamic neurons induces cortical Down transition in naturally sleeping mice. Optogenetic stimulation of MTN neurons terminates Up states, while MTN silencing prolongs Up states in both anesthetized and naturally sleeping mice. The thalamus-induced Down transition is mediated via Layer 1 neurogliaform interneurons acting on cortical $GABA_B$ receptors. MTN synchronize slow waves across cortical areas during natural sleep.

**Conclusions:** These results strengthen the evidence that thalamocortical interactions are essential for the full expression of slow-wave sleep and show that Down transition is an active process mediated by cortical $GABA_B$ receptors.

**Disclosure**: No

## O141/P940 | Sleep related rhythmic disorder in young children with down syndrome: prevalence and clinical features

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**Introduction:** Sleep-related Rhythmic Movement Disorder (RMD) affects around 1% of UK pre-school children. It is a poorly understood sleep-related movement disorder, commonly believed to be benign and self-limiting. Little is known about RMD in Down syndrome (DS).

**Aims:** We aimed to determine: (a) the prevalence of RMD in children with DS aged 1.5–8 years; (b) phenotypic and sleep quality differences between children with DS and RMD and sex- and age-matched DS controls; and (c) night-to-night variability in rhythmic movements (RMs).

**Methods**: Setting: A UK DS research registry of 202 children who had previously participated in a prevalence study of sleep apnoea.

Parents were contacted and, if clinical history suggested RMD, visited at home. Infra-red home videosomnography over 3 nights confirmed the presence of RMs. Actigraphy (MicroMini-Motionlogger® Actigraph, AMI, NY) for 5 nights assessed sleep efficiency. Data were analysed using Action W2.7 software (Sadeh algorithm). Phenotype was explored through parent completed questionnaires: demographic data, the strengths and difficulties questionnaire to screen for behavioural difficulties, the Q-CHAT-10 or social communication questionnaires to assess Autism Spectrum features and the life events questionnaire to explore exposure to adversity. Index cases were matched with an age-similar, same sex controls and all measures, other than home video, were completed.

**Results**: Eight children (4M) had confirmed RMD, mean age 54.8 months (SD. 21.2). To account for non-participation, minimal (identified cases) and estimated maximal prevalence (all possible cases) were computed. These were 4.10% and 15.38%, respectively. Controls (4M) had mean age 56.0 months (SD 20.7), not significantly different to cases. Sleep efficiency was significantly lower in RMD-cases (69.1%) versus controls (85.2%), with no significant differences in total sleep time and no other phenotypic differences. There was considerable intra-individual night-to-night variability in RMs based on home videosomnography assessment.

**Conclusion:** RMD is significantly more prevalent in children with DS than in the young child population as a whole, varies from night to night and is associated with significantly worse sleep quality. No daytime phenotypic differences were associated with RMD in this small sample. Children with DS should be screened for RMD, which is amenable to treatment.

**Disclosure**: Yes

**Conflict of Interest statement:** I have received unrestricted educational grants from Flynn Pharma, UK and fees for expert advisory panel work for Neurim Pharmaceuticals, Israel.

## O048/P941 | The impact of smartphone use and short-wavelength light during the evening on sleep, circadian rhythm and cognitive performance

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We here present our study investigating the effects of short-wavelength light from a smartphone during the evening on sleep and circadian rhythms. 33 healthy male adult subjects (mean age: 21.70 years, standard deviation: 1.91 years) participated in our within-subjects design where polysomnography and body temperature were recorded throughout one adaptation and three experimental nights. The light conditions were counterbalanced across the three nights. Cortisol, melatonin and affectivity (PANAS scale) were assessed before and after sleep. Subjects had to perform a declarative word-pair-association task as well as a Go/Nogo task which was presented in total four times per night. Further they read for 90min on a standardized smartphone (Samsung Galaxy A50) with or without a filter or from a book before going to bed during the experimental nights. Our results indicate reduced slow-wave-sleep and slow-wave-activity in the first night quarter after reading on the smartphone without a filter. Additionally a weaker cortisol-awakening-response was revealed after short-wavelength light exposure. Although subjective sleepiness (Karolinska Sleepiness Scale) was not affected, the evening melatonin increase was attenuated in both smartphone conditions. Accordingly, the distal-proximal skin temperature gradient increased less after short-wavelength light exposure than after reading a book. Interestingly, we could unravel that higher positive affectivity in the evening predicted better subjective but not objective sleep quality. Our results show disruptive consequences of short-wavelength light for sleep and circadian rhythmicity with a partially attenuating effect of blue-light filters. Furthermore, affective states influence subjective sleep quality and should be considered, whenever investigating sleep and circadian rhythms.

**Disclosure**: No

## O075/P942 | Rem sleep behavior disorder: from parasomnia to topic of hope in neuroscience

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Among the parasomnias, RBD is the one that requires polysomnography for diagnosis, because only with PSG the characteristic electromyographic findings can be documented, whereas the manifold types of vocalizations, body jerks, and apparently dream-enacting behaviors of RBD could also occur in other conditions which mimic RBD.

The importance of RBD to neuroscience has become apparent, when Mahowaland Schenck, and later multiple others have noted that the majority of patients with initially clinically isolated REM sleep behavior disorder over a course of years or decades will convert to overt alfa-synuclein-related neurodegenerative disease (PD/DLB/MSA). Even in isolated (formerly "idiopathic") RBD at thorough neurological, neuropsychological or imaging evaluation, presence of neurodegeneration in the brain is evidenced. Therefore, for patients diagnosed with iRBD, it is important to know if they are at risk for imminent conversion into symptomatic alpha-synuclein related disease, and in this context biomarkers come into play. Multiple biomarkers of neurodegeneration have been described in iRBD, and classified for different purposes, several large reviews have summarized recent developments.

Over this exciting and emerging field of new biomarkers, sleep specialists are aware that *polysomnography is not only the diagnostic instrument to diagnose RBD, but is also a sensitive and specific biomarker itself*. In particular, EMG activity during REM sleep has been shown to be a quantifiable biomarker of the disease, different central pathways generate different types of EMG activity and evidence accumulates that EMG activity progresses with disease duration, and there is even a phase of prodromal RBD.

The fact that isolated RBD precedes manifest daytime alpha-synuclein disease by more than a decade, *leads to the situation that sleep physicians are usually the first clinicians who see those patients*. While disease modifying treatments for RBD and alpha-syuncleinopathies have not yet been established, good clinical follow up and counselling regarding lifestyle factors are important, and symptomatic treatments are available. In the near future, well diagnosed RBD patients are likely to have a higher chance of benefitting from disease modifying treatments, because the neurodegenerative process is in a much earlier stage than

in patients with already manifest alpha-synuclein related disease, namely PD or DLB.

**Disclosure**: No

## O143/P943 | The effects of sleep disordered breathing in children with down syndrome: does treatment improve cardiovascular control?

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**Objective:** Sleep disordered breathing (SDB) in typically developing (TD) children is associated with adverse cardiovascular effects. As children with Down syndrome (DS) are at increased risk for SDB, we aimed to compare the cardiovascular effects of SDB in children with DS to those of TD children with and without SDB. Additionally, we aimed to examined the effects of treatment on cardiovascular control in the children with DS.

**Study Design:** 44 children with DS (3–19 years) were age and gender matched with 44 TD children without SDB (TD-) and with 44 TD children with matched severity of SDB (TD+). BMI, systolic and diastolic *z*-scores were calculated. Heart rate variability (HRV) was calculated for 2 min artefact free epochs overnight. Power spectral density for the low frequency (LF), high frequency (HF), total power (TP) and the LF/HF ratio (sympathovagal balance) were calculated. Data were compared between groups with Kruskal-Wallis one-way ANOVA. 24 children with DS returned for a follow-up study. Children were grouped into Improved ($n = 12$) and Unimproved ($n = 12$) groups for analysis of baseline and follow up data.

**Results:** Wake heart rate, systolic and diastolic *z*-scores were not different between groups. Children with DS had higher HF power, a measure of parasympathetic activity, and lower sympathovagal balance during sleep and when awake. There were no differences between groups for LF power. $SpO_2$ nadir, average $SpO_2$ drop and $SpO_2$ > 4% drop were larger in the DS group compared to the TD+ group ($p < 0.05$ for all). At follow-up in the DS Unimproved group during N3 and Total Sleep, LF Power was lower at follow up compared with baseline ($p < 0.05$), indicating dampened sympathetic and parasympathetic activity and in REM, HF Power also decreased from baseline to follow up indicating dampened parasympathetic activity ($p < 0.05$).

**Conclusions:** Our findings demonstrate significantly reduced parasympathetic activity (reduced HF power) and increased sympathovagal balance in children with DS, together with greater exposure to hypoxia, suggesting SDB has a greater effect in these children that may contribute to an increased risk of adverse cardiovascular outcomes. Autonomic dysfunction worsened in children with DS whose SDB had not improved by at least 50%, two years following a baseline study, irrespective of treatment status. Autonomic function remained unchanged in children whose SDB had improved, suggesting that an improvement in SDB severity prevents worsening of autonomic dysfunction. These results further support the need for children with DS to be investigated for SDB in the clinical management of their cardiovascular health.

**Disclosure**: No

## O140/P944 | Thalamocortical activity during stress-induced sleep disturbance

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Behavioral and sleep disorders caused by stress affect millions of people around the world, but its neurobiological bases are still unclear. The calretinin-positive neurons of the paraventricular thalamus (PVT/CR+) are in a unique position to participate in stress induced sleep disturbances since they receive selective inputs from all major stress and arousal center and project to the main forebrain regions involved in fear, anxiety and behavioral control. Furthermore, activity of PVT/CR+ cell is significantly affected both by stress and sleep-wake transitions.

Based on these, in this study we tested whether post-stress activity of PVT/CR+ neurons contributes to the acute stress-induced changes in sleep behavior of mice. To this end we inhibited PVT/CR+ neurons after an exposure to a natural stressor (fox odour, 2MT) using cell type specific optogenetic inhibition (SwiChR) and measured nesting behavior, locomotion, sleep, and stress hormone levels. EYFP injected animals served as controls.

Following the stress exposure, the uninhibited, EYFP group displayed increased EMG activity, disturbed sleeping behavior, and elevated corticosterone level. The behavioral changes persisted for five days following the stress exposure. Photoinhibition of PVT/CR+ cells once for one h after the stress prevented all these changes, with the exception of acute hormonal stress response.

We also aimed to determine the activity of PVT/CR+ cells before and after the exposure to the stressor. During pre-stress days PVT/CR+ cells displayed strongly state dependent activity. Following the exposure to the stressor the firing rate and pattern as well as the state dependent activity of PVT/CR+ cell were significantly altered for five days with strongest increase in the nest and during sleep. We also tested whether stress induced long term changes in firing activity can be reversed by post-stress photoinhibition. We found that photoinhibition of PVT/CR+ neurons after the 2MT presentation, prevented the altered firing rate and state dependence, the increase in high frequency clusters and cross correlations during the post-stress days strongly supporting the behavioral data.

These data together strongly suggest that post-stress activity of PVT/CR+ cells is crucial to establish the neuronal network responsible for the emergence of acute stress induced alteration of sleeping behavior.

**Disclosure**: No

## O229/P945 | Vestibular problems and sleep quality in a population-based sample

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**Introduction:** Dizziness is a physical and mental burden that affects 33% of the older population. Only few of those suffering from dizziness seek help in a specialized clinic. Studies investigating dizziness patients in vestibular clinics show that many also report sleep problems. How the sleep-dizziness link is represented in the general middle-aged and older non-clinical population is however not well known.

**Objectives:** The objective of this study was to estimate the association between self-reported and actigraphy-estimated sleep and dizziness in a population-based sample. Further, we aimed to investigate whether this link differs between dizziness from assumed vestibular origins or from assumed non-vestibular origins.

**Methods:** In 4702 participants of the Rotterdam Study, sleep quality was measured with the Pittsburgh Sleep Quality Index while dizziness was measured by response scores on 19 clinical dizziness questions. Data were collected between February 2011 and June 2014. A subset of data from 1440 participants containing information from actigraphy was further analyzed, investigating total sleep time, sleep efficiency, sleep onset latency and wake after sleep onset. The association between sleep and dizziness was assessed using logistic regression, adjusting for multiple covariates.

**Results:** In this sample, the mean age was 65.8 (± 7.9) years old and 55.7% of them were women. A poor self-reported sleep quality was associated with higher odds of dizziness (OR = 1.065, 95% CI: 1.043 to 1.087, $p < 0.001$) after adjusting for confounders. Only dizziness with a possible non-vestibular origin was linked to sleep. None of the actigraphy-estimated sleep parameters was associated with dizziness. Results did not change when analyses were repeated in a subsample limited to individuals without clinically relevant anxiety and/or depressive symptoms and when stratifying by sex.

**Conclusions:** We show that poor self-reported sleep quality, but not objective estimates of sleep, is associated with increased experience of dizziness in a population-based sample. The link between sleep problems and non-vestibular dizziness requires further investigation. The findings might encourage clinicians to assess dizziness in the sleep clinic, since the relation with sleep appears direct and not just depending on psychiatric symptoms.

**Disclosure**: No

## O134/P946 | Challenges in the diagnosis and management of obstructive sleep apnea syndrome in children

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**Introduction:** In 2016–2017, two ERS Statements summarized the evidence and currrent practice on the diagnosis and management of obstructive sleep apnea syndrome (OSAS) in children aged 1 month to 18 years.

**Objectives:** The aim of this presentation is to review evidence published over the last 6 years that addresses knowledge gaps in the pathogenesis, diagnosis and management of OSAS in children.

**Results:** *1. Pathogenesis*. Circulating plasma extracellular vesicles (exosomes) are involved in cell-to-cell communication and in children with OSAS potentially disrupt the integrity of the blood-brain barrier and exert adverse effects on endothelial wound healing, especially among individuals with neurocognitive deficits. *2. Diagnosis*. There is an urgent need for the development of reference values for respiratory polysomnography parameters in the first year of life. Currently proposed upper reference value for obstructive apnea–hypopnea index (AHI) ranges from 5.8 episodes/h at 1 month of age to 3.6 episodes/h at 1 year. These values were calculated without considering hypopneas accompanied by EEG arousals.*3. Management*. Behavior, OSAS-related symptoms and quality of life improve post-adenotonsillectomy (post-AT) even in children with AHI 1-5 episodes/h. Resolution of enuresis is accelerated postoperatively and office-measured blood pressure decreases in patients with OSAS and hypertension. Favorable AT effects have been reported in children with very severe (AHI > 20 episodes/h) and extremely severe OSAS (AHI > 100 episodes/h), without postoperative mortality, need for endotracheal intubation, prolonged hospitalization or re-admission after hospital discharge. Nevertheless, the frequency of residual OSAS post-AT may reach 30%–60%. Which children younger than 2 years should undergo AT instead of adenoidectomy only, to prevent recurrence of OSAS symptoms and revision surgery remains unclear. Of note, the evidence regarding undesirable increase in body weight among school-age children post-AT (i.e., classification of a normal-weight or underweight child preoperatively as overweight postoperatively) is conflicting. Comorbid central sleep apnea (central apnea index ≥1 episode/h) in children with OSAS usually resolves postoperatively. AT in children with Prayer-Willi syndrome is frequently accompanied by postoperative residual OSAS while complications are not uncommon.

**Conclusion:** In the last 6 years, several studies have addressed controversies in the pathogenesis, diagnosis and management of OSAS in childhood.

**Disclosure**: No

## O052/P947 | Pathways from prenatal and postnatal stress to sleep across childhood

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**Introduction:** Early life stress is robustly associated with poor sleep across life. Preliminary studies suggest that these associations may begin already in utero.

**Objectives:** We study the longitudinal associations of prenatal psychosocial stress with sleep across childhood, and assess whether prenatal stress interacts with genetic liability for poor sleep.

**Methods:** The study is embedded in the Generation R population-based birth cohort. Caregivers reported on prenatal psychosocial stress (life events, contextual, parental or interpersonal stress) and on children's sleep at ages 2 months, 1.5, 2, 3 and 6 years. The study sample consisted of 4,930 children; polygenic risk scores for sleep traits were available in 2,063.

**Results:** Prenatal stress was consistently associated with more sleep problems across assessments. Effect sizes ranged from small ($B = 0.21$, 95%CI: 0.14; 0.27) at 2 months to medium ($B = 0.45$, 95% CI: 0.38; 0.53) at 2 years. Prenatal stress was moreover associated with shorter sleep duration at 2 months (Bhrs = −0.22, 95%CI: −0.32;−0.12) and at 2 years (Bhrs = −0.04, 95%CI - 0.07; −0.001), but not at 3 years (Bhrs = 0.02, 95%CI: −0.02;0.06). Prenatal negative life events interacted with polygenic risk for insomnia to exacerbate sleep problems at 6 years (Binteraction = 0.07, 95%CI: 0.02; 0.13).

**Conclusions:** Psychosocial stress during pregnancy has negative effects on children's sleep that persist across childhood, and are exacerbated by genetic liability for insomnia. Effects on sleep duration were more pronounced in infancy and seem to attenuate with age. These findings highlight the role of the prenatal environment for developing sleep regulation, and could inform early intervention programs targeting sleep in children from high-risk pregnancies.

**Disclosure**: No

## O227/P948 | Rhythmic mechanosensory stimulation of the vestibular system promotes sleep in mice

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The potential of sensory modulation of sleep has been under the scope of sleep researchers and clinicians for several decades. Nevertheless, the mechanism by which the vestibular system contributes to the tuning of adult sleep behavior remained elusive, particularly in species other than human. Thus, we first set out to investigate the effect of rhythmic mechanosensory vestibular stimulation, or "*rocking*", on adult mouse sleep. Indeed, mice rocked at 1.0 Hz during the 12-h light period spent more time in NREM sleep at the expense of wakefulness, compared to their respective stationary baselines. This effect was not observed when using 0.25 or 0.5 Hz, while it was even larger at 1.5 Hz. However, this higher rocking frequency suppressed REM sleep. Analysis of sleep architecture revealed that rocking favored wake-to-NREM-sleep transitions and shortened sleep-onset latency, while maintenance of sleep was not affected. Interestingly, while NREM-sleep EEG was not affected at the 3 lower frequencies tested (0.25, 0.5, and 1.0 Hz), it was largely impacted at 1.5-Hz rocking, where a reduction throughout the delta band was observed. Additionally, theta peak activity, particularly during wakefulness, was consistently shifted towards lower frequencies during rocking at 1.0 and 1.5 Hz. Perhaps most importantly for future applications, the peripheral vestibular organs encoding linear acceleration appear to be responsible for the mediation of the effects, since none were observed in mice without a functional otolithic system, compared to their littermates. To clarify which aspect of rocking was mediating the observed effects, rocking frequency was kept constant at 1.0 Hz, while different rocking amplitudes were tested to match the accelerations in the first cohorts. This last set of experiments revealed that the key parameter encoding the rocking effect was indeed linear acceleration, and not frequency, which also provides an explanation for the discrepancies observed between human vestibular-stimulation studies. To conclude, rocking induces NREM sleep not only in humans, but also in mice, mainly through the otolithic organs of the vestibular system.

**Disclosure**: No

## O194/P949 | Maturation of sleep-gut microbiome dynamics in infancy and links to behavioral development

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The sleep-gut-brain axis is lately gaining much attention. While its bi-directionality has been demonstrated in animal models and adult humans, it is yet largely unclear how the sleep-gut link evolves in the early period of human life.

Habitual sleep behaviors in early life relate to later maturational outcomes, and also sleep neurophysiology entails hallmarks of brain maturation processes. Further, compelling evidence is piling up that gut microbiota also play a pivotal role in human brain development.

We conducted an interdisciplinary investigation to generate longitudinal data in 162 healthy infants. Results unravel a sleep-brain-gut relationship on several levels: sleep habits and gut microbiota, gut microbial profiles and sleep EEG neurophysiology, and the connection of sleep habits and bacterial markers with behavioral-developmental outcomes.

We gain three interesting insights: First, the strongest linkages between sleep habits, gut microbiota, and behavioral outcomes were found at 3 months of age, potentially identifying an early sensitive period for later functionality of sleep rhythm and gut microbial balance. Second, for both sleep habits and gut microbiota, the general pattern emerged that concurrent associations with behavioral development were stronger than predictive associations. Third, infant sleep neurophysiology (EEG), predicts later gut microbiome, representing a top-down dynamic within the sleep- brain-gut framework. This confirms the newly emerging concept of a sleep-brain-gut axis - now also in infancy.

Poor sleep and poor nutrition in early life can equally severely affect later child development, and many adult diseases root in early childhood. Yet, both, sleep and gut microbiota can be readily modified, and leveraging protective factors of sleep-and gut-norms could constitute health promoting factors across the human lifespan.

**Disclosure**: No

## O219/P950 | Early sleep and circadian markers of alzheimer's disease: the impact of apoe- ε4 on sleep-wake regulation, brain activity and cognition in humans

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**Introduction:** Sleep deficits have been linked to dementia including Alzheimer's disease (AD). The*APOE-ε4* allele, the genetic risk factor of AD, has been shown to modulate some of these associations albeit with a considerable discrepancy between studies.

**Objectives:** We set out to investigate the effects of the*APOE-ε4*status on sleep-wake regulation using observational and experimental study designs in healthy elderly adults.

**Methods:** In total 161 participants (117 female) between 42 and 90 years old have taken part in extensive screening sessions (51 *APOE-ε4*$^+$, 110 *APOE-ε4*$^-$) of which 58 (28*APOE-ε4*$^+$, 30*APOE-ε4*$^-$) participated in a 14-days-long actigraphy session. Thirty-five individuals (18*APOE-ε4*$^+$, 17*APOE-ε4*$^-$) underwent a 2.5-days-long laboratory session in dim light conditions (<10lx). After a baseline night, participants were randomly assigned to either a 40-h sleep deprivation (SD) or a multi-nap(MN) experimental condition followed by a recovery night. Nine 80-min-long naps were scheduled every 4 h in the MN condition. Vigilance, cognition, EEG activity, and postural control (i.e., measured by posturography) were measured on a 4-hourly basis in both experimental conditions.

**Results:** There were no significant genotype differences in either self-reported or polysomnography measured sleep. There was a significant decrease in the actigraphy-measured circadian rest-activity relative amplitude (RA) in the *APOE-ε4*$^+$ subgroup. The genotype did not significantly modulate the effect of sleep loss and circadian phase on cognition. Interestingly the negative effect of sleep loss on balance control was modulated by both sex and *APOE* status. Men and *APOE-ε4* carriers were more affected after sleep loss when both visual and haptic sensorial feedback was provided. Lower self-reported sleep quality was the strongest predictor of worse mental health, independent of age, sex, *APOE-ε4* carriership, and other confounding factors. However, this association was stronger in men and *APOE-ε4* carriers compared to non-carriers. The known association between increased eveningness and lower subjective sleep quality was present in non-carriers only.

**Conclusion:** *APOE* is not linked to individual vulnerability to sleep loss but modulates the amplitude of the circadian rest-activity rhythmicity, the effect of sleep deprivation on postural control, and the associations between sleep, brain activity, and mental well-being and cognition in healthy older adults.

**Disclosure**: No

## O057/P951 | And if there was no such thing as a nrem-rem ultradian cycle?

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**Introduction:** The alternation of NREM and REM sleep has, since 1953, been the subject of numerous hypotheses, but all, to our knowledge, use the concept of cycles. Two issues deserve attention: (1) Cycles require, at a minimum, a sequence of events where each element calls for the next, and a return to baseline is eventually achieved. What immediately follows a REM episode (REM-Off) is, however, twofold, as it can be either wakefulness or NREM sleep. As these are quite distinct physiological states, this makes it difficult to establish a repetitive sequence; (2) Even using flexibility, it is often difficult to integrate long REM-REM intervals.

**Objectives**: To present an alternative hypothesis to NREM-REM cycling, using the recent concept of post-REM refractory period (PRRP).

**Methods**: Based on the observation that REM episodes never seem to exceed a species-specific duration, I postulated that REM episodes terminate their own activity when they have not been interrupted, before this maximum duration, by awakenings or NREM. If they do so, a refractory period is logically necessary to prevent the resumption of

REM sleep. A similar concept was introduced in the Short- and Long-term hour glass hypothesis.

**Results**: A refractory period after a REM episode creates the illusion of a cycle, as NREM will inevitably reappear at some point, most likely related to its relationship with Wake. The "Long-term homeostasis" takes care of the infradian influences: according to the respective consolidated pressures for NREM and REM, a REM episode occurs when three conditions are met: (1) a NREM episode large enough to be interrupted by REM-On cells, (2) a sufficiently high REM pressure; (3) not within a PRRP period. Instead of cycling, we have a succession of NREM-REM-PRRP triads on a background of flexible exchanges between NREM and Wake. Concerning the two objections cited above: (1) there is no need for a repetitive sequence since no cycling is invoked; (2) long intervals only mean that the three conditions have not been met.

**Conclusions**: In the Asymmetrical (or Linear) hypothesis presented here, the onset of REM would be conditional and local, while giving the illusion of a NREM-REM cycling.

**Disclosure**: No

## O043/P952 | Cerebral glucose metabolic damage and neurodegeneration in patients with osa and the beneficial role of cpap therapy

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Obstructive sleep apnea (OSA) is the most frequent sleep-disordered breathing and is presenting an increasingly common prevalence in the adult and elderly populations. It has been already established that OSA represents a risk factor for cognitive impairment and dementia, in particular Alzheimer's disease (AD). Several biomarkers of neurodegeneration have been evaluated in patients with OSA, and signs and symptoms of cognitive impairment have been identified in those patients. Cerebral glucose metabolism can be *in vivo* studied by using nuclear medicine instruments (such as positron emission tomography - PET) and the other biomarkers of neurodegeneration can be investigated by cerebrospinal-fluid (CSF) analysis. Consistently, biomarkers of neurodegeneration can be modified by continuous positive airway pressure (CPAP) treatment in patients with OSA, as well as cognition can be improved. Notably, our group recently documented that the alteration of cerebral glucose metabolism in patients with OSA correlated with the increased total and phosphorylated tau protein CSF levels. However, this cerebral glucose metabolism impairment can be partially restored by 12-months CPAP treatment. In this presentation, studies about cognition, cerebral glucose metabolism and CSF biomarkers of neurodegeneration in patients with OSA will be presented, also in relation with the beneficial effect of long-term CPAP treatment.

**Disclosure**: No

## O113/P953 | Sleep and alzheimer disease

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Sleep disturbances increase with age, and sleep disturbances likely directly contribute to the pathology seen in Alzheimer's Disease (AD). Interventions that improve sleep may be a tractable approach to preventing or slowing the progression of AD. We have shown that broad spectrum morning bright light therapy improves both subjective and objective measures of sleep disturbances in older individuals, likely through short wavelength activation of melanopsin-sensitive intrinsically photosensitive retinal ganglion cells (ipRGCs). However, traditional light therapy has been limited to cumbersome devices such as the light box, which limits the individual to a fixed spectrum at a fixed time of day, and has poor acceptability due to restricted mobility during use. The advent of tunable LED lamps which can be embedded within native home lighting systems provides a potential solution to this problem. We hypothesized that tunable LED lighting that maximizes short-wavelength light in the morning and minimizes short-wavelength light in the evening, would improve long-term sleep in the home. In order to test this hypothesis, we first performed a proof-of-concept, feasibility study using participants with embedded home assessment platforms who were enrolled in an existing study at Oregon Health & Science University (e.g., LifeLab at ORCATECH/OHSU Layton Center for Aging and Alzheimer's) that included long-term continuous data collection of room location, activity, sleep, and general health parameters are collected at minute-to-minute resolution over years of participation. This single arm longitudinal protocol collected participants' light usage and light exposure over a several month period before and after light installation. The protocol was implemented with 4 subjects living in 3 ORCATECH homes. An additional 10 ORCATECH homes received custom-designed wall-mounted light sensors to measure red-green-blue (RGB) spectral light exposure from multiple rooms of each home. The successful implementation of both our light intervention and light sensing protocols supports the feasibility of integrating tunable whole-home lighting systems into an automated home-based assessment platform for continuous data collection of outcome variables, including long-term sleep measures. This protocol could inform the implementation of future clinical intervention trials using light therapy in patients at risk for developing Alzheimer's Disease and related conditions.

**Disclosure**: No

## O044/P954 | The cognitive benefits of napping in sleep-restricted adolescents

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**Introduction:** Sleep curtailment is common among adolescents, particularly on school nights, because of maturational and social changes, as well as early school start times. Yet, recent studies have shown that adolescents are not spared from the cognitive deficits induced by partial sleep deprivation.

**Objectives:** Vigilance deficits were characterised during recurrent sleep restriction among adolescents, and the effectiveness of afternoon napping in alleviating such decrement was examined.

**Methods:** In the Need for Sleep studies, 194 adolescents (age = 15–19 years) underwent two baseline nights of 9-h time-in-bed (TIB), followed by two cycles of weekday manipulation nights and weekend recovery nights (9-h TIB). They were allocated 9, 8, 6.5, or 5 h of TIB for nocturnal sleep on weekdays. Three additional groups with 5-h or 6.5-h TIB were given an afternoon nap opportunity of either 1 h or 1.5 h (5 + 1 h, 5 + 1.5 h, and 6.5 + 1.5 h). A 10-min Psychomotor Vigilance Task was administered three times daily, and the daily average of the number of lapses (responses > 500 ms) was used as a measure of vigilance.

**Results:** The number of PVT lapses of the 9 h and the 8 h groups was comparable and remained at baseline levels throughout the study. Vigilance deficits were greater among the 5 h and the 6.5 h groups, were more prominent in the second than the first week of sleep restriction despite partial recuperation during the intervening recovery period, and diverged between these two groups during the second cycle. Napping in the afternoon significantly reduced the number of lapses among the adolescents with curtailed nocturnal sleep opportunities.

**Conclusions:** Even with recovery sleep opportunities over the weekend, vigilance decrement accumulates across multiple weeks when adolescents' weekday TIB is shortened beyond the minimum recommended duration of 8 h. Such decrement can be effectively ameliorated by afternoon napping.

**Disclosure**: No

## O051/P955 | Sleep and hpa-axis stress response in middle-aged and older persons

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**Introduction:** Poor sleep is common in the general population, with hyperarousal and stress often suggested as causal factors. Conversely, sleep might also affect the stress response, in which the hypothalamic-pituitary-adrenal (HPA) axis plays a key role.

**Aims:** To improve insight into the role of sleep in functioning of the negative feedback loop of the stress system, we assessed (1) the cross-sectional and longitudinal associations between actigraphy-estimated sleep and cortisol response to dexamethasone over time and (2) the cross-sectional association between PSG-estimated sleep and cortisol response to dexamethasone.

**Methods:** Between 2004–2007, sleep and 24-h activity rhythms were estimated with actigraphy (mean: 146 ± 19.6 h) and the Pittsburgh Sleep Quality Index in 410 participants (age: 56.1 ± 5.5 years, 59% women) of the population-based Rotterdam Study. To assess the function of the negative feedback loop of the HPA axis, we measured cortisol before and after the intake of a very low-dose of dexamethasone (0.25 mg). For 217 participants, the cortisol response to dexamethasone was assessed again after 5.7 years (IQR = 5.5–5.8). Between 2012 and 2014, sleep was also assessed using polysomnography in 403 participants (age: 62.4 ± 5.0 years, 55% women). We used linear regression and linear mixed models.

**Results:** First, long sleep onset latency ($B = -0.01$, 95% CI = −0.01; 0.00), unstable ($B = 1.72$, 95%CI = 0.80; 2.64) and fragmented ($B = -1.48$, 95%CI = −2.42; −0.54) 24-h activity rhythm were cross-sectionally associated with an enhanced response to dexamethasone, that is, a stronger suppression of cortisol by the HPA axis. Second, unstable ($B = 1.64$, 95%CI = 0.78; 2.50) and fragmented ($B = -1.31$, 95%CI = −2.17; −0.45) 24-h activity rhythms, and apoor self-rated sleep quality ($B = -0.02$, 95%CI = −0.04;0.00), were also associated with an enhanced response to dexamethasone over time. Third, short N2 sleep ($B = 0.005$, 95%CI = 0.002; 0.009) and long N3 sleep ($B = -0.007$, 95%CI = −0.010; −0.003) were additionally cross-sectionally associated with an enhanced response.

**Conclusions:** We demonstrated a cross-sectional association of indicators of poorer sleep and 24-h rhythms with an enhanced response to dexamethasone, that is, stronger suppression of cortisol. Furthermore, some of these associations are remain over a follow-up of multiple years. These findings provide further support that sleep is not only affected by the stress system but that it in turn sleep may also affect our HPA axis, even over longer periods of time.

**Disclosure**: No

## O135/P956 | The peculiar interplay of rls, sleep and pregnancy: the life-on project

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Pregnancy is a risk factor for a new onset and often-transient form of RLS or for a worsening of a pre-existing RLS. The mean prevalence of RLS during pregnancy ranges between 20% and 25%. Pregnancy-related RLS peaks in the third trimester of gestation, herein affects up to 30% of women. RLS symptoms improve or disappear soon after delivery. Women affected by a pre-existing form (before pregnancy) worsen in severity of symptoms during pregnancy and are more prone to persist with symptoms after delivery, compared to those with a new-onset RLS during pregnancy. The mechanism behind RLS during pregnancy is still unclear. A genetic

predisposition of affected women is postulated, since women who experience RLS during pregnancy are more prone to develop an idiopathic form of RLS later on in their life. With the Life-ON project, we prospectively assess face to face RLS during pregnancy and postpartum in 439 women (mean age 33.7 ± 4.2 y) during pregnancy and 1 year postpartum. Prevalence of RLS during pregnancy was 27%, with a peak in the third trimester. This study also provided the largest polysomnographic dataset during pregnancy, finding a PLMS index larger than 4 in 55% of women in the second trimester of pregnancy. Among women affected by RLS in the third trimester, 19% reported their symptoms as severe. RLS prevalence dropped to 5% in postpartum. An accurate diagnosis helps to early recognize the syndrome and choose the optimal therapeutic strategy, based on the characteristics and needs of the patient, in according with the consensus clinical guidelines.

**Disclosure**: No

## O062/P957 | A new electrophysiological fingerprint in sleep apnea patients

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**Introduction:** Obstructive sleep apnea (OSA) is associated with sleep-stage- and respiratory-event-specific sensorimotor cortico-muscular disconnection. The modulation of phase-amplitude cross-frequency coupling (PACFC) may influence information processing throughout the brain.

**Objective:** We investigated whether sleep-stage-specific PACFC is impaired at the sensorimotor areas in OSA patients.

**Methods:** C3 and C4 electrode EEG polysomnography recordings of 170 participants were evaluated. Different frequency band combinations were used to compute CFC modulation index (MI) to assess if MI differs between OSA and non-significant OSA patients in distinct sleep stages. We tested if the CFC-MI could predict daytime sleepiness in OSA.

**Results:** Theta-gamma CFC-MI at cortical sensorimotor areas was significantly reduced during all sleep stages; the delta-alpha CFC-MI was significantly reduced during REM and N1 while increasing during N2 in patients with respiratory disturbance index (RDI); 15/h compared to those with RDI ≤15/h. A sleep stage classification using MI values was achieved in both patient groups. Theta-gamma MI during N2 and N3 could predict RDI and Epworth Sleepiness Scale, while delta-alpha MI during REM predicted RDI.

**Conclusion:** This increase in disconnection at the cortical sensorimotor areas with increasing respiratory distress during sleep supports a cortical motor dysfunction in OSA patients. The MI provides an objective marker to quantify subjective sleepiness and respiratory distress in OSA.

**Disclosure**: No

## O114/P958 | Sleep and parkinson disease

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In Parkinson's disease (PD) is characterized by damaging intracellular α-synuclein (αSyn) deposition that propagates extracellularly contributing to disease spread. Intracellular αSyn is sensitive to degradation, whereas extracellular αSyn may be eliminated by glymphatic clearance, a process shown in rodents to be increased during slow-waves sleep (SWS). Also, SWS appears to be closely linked with the velocity of progression of the disease motor symptoms and pharmacologically enhancing SWS results in objectively and subjectively improved sleep scores in PD patients. Here, we explored whether long-term slow-wave modulation in murine models of PD presenting αSyn aggregation alters pathological protein burden and, thus, might constitute a valuable therapeutic target.

In a recent study, we exerted slow-waves enhancement in VMAT2-deficient and A53T mouse models of PD by twice daily administration of sodium oxybate (200 mg/kg, p.o.) 5 days/week for 4 months. Slow-waves deprivation in VMAT2-deficient mice consisted of 16 h/day sleep deprivation using the platform-over-water method. We the performed multiple histopathological, immunofluorescence, biochemical, and molecular analyses over brain samples from sleep-modulated healthy and PD mice to asses αSyn protein load and the potential mechanisms associated to its alteration upon sleep modulation.

Sleep-modulating treatments showed that enhancing slow waves in both VMAT2-deficient and A53T mouse models of PD reduced pathological αSyn accumulation compared to control animals. Non-pharmacological sleep deprivation had the opposite effect in VMAT2-deficient mice, severely increasing the pathological burden. Regarding potentially involved mechanisms, we found that SWS enhancement via sodium oxybate was associated with increased recruitment of aquaporin-4 to perivascular sites, suggesting a possible increase of glymphatic function. Furthermore, mass spectrometry data revealed differential and specific upregulation of functional protein clusters linked to proteostasis upon slow-wave-enhancing interventions.

Overall, the beneficial effect of SWS enhancement on neuropathological outcome in murine synucleinopathy models mirrors findings in models of Alzheimer and encourage further preclinical and clinical studies unraveling the sleep-based interventions as potential therapeutic in PD.

**Disclosure**: No

## O055/P959 | Short- and long-term hourglass processes in rem sleep chronobiology

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**Introduction:** The stability of the daily REM sleep (REMs) quota may rely on to two different hourglass processes: a long-term hourglass that keeps track of the cumulated amount of REMs, and a short-term hourglass related to the periodic occurrence of REMs within the ultradian sleep cycle. A closed loop long-term REMs hourglass mechanism may explain the REMs rebound and recovery that are proportional to the magnitude of REM sleep loss as documented in animal models. The short-term REMs hourglass was proposed to explain the positive correlation observed between REMs episode duration and the subsequent intervals without REMs. The short-term hourglass may also correspond to a closed loop (homeostatic) mechanism where REMs propensity accumulates along the interval and dissipates during the REMs episode.

**Objective:** To obtain evidence for a REMs refractory period occurring after prolonged REMs episodes in rats and degus as has been recently described in mice.

**Methods:** Two-hour total or selective REMs deprivation combined with intermittent REMs deprivation in 15 rats. Log-normal mixture model-based analysis on polysomnographic data of undisturbed days of 32 rats and 15 *Octodon degus*.

**Results:** Complete REMs recovery and equivalent values of REMs propensity parameters were obtained after total or REMs selective deprivation in the rat. Durations of interval without REMs are appropriately described by two log-normal curves corresponding to short and long intervals. The long-interval distribution is shaped by a post-REMs episode refractory period that depends on the duration of the REMs episode in rats and degus.

**Conclusions:** REMs debt is by itself necessary and sufficient to explain the buildup of REMs propensity and subsequent recovery, where REMs propensity accumulates in the absence of REMs and dissipates during REMs. The fulfillment of the REMs quota occurs by the enhancement of REMs transition probability and consolidation of REMs episodes. The short-term process may operate as an open-loop mechanism activated during consolidated REMs episode and released as a REMs refractory period during the following interval. The REMs refractory period may be a self-limiting mechanism that, by suspending REMs expression, allows the regular occurrence of wake or NREM sleep bouts under high REMs propensity.

**Disclosure**: No

## O116/P960 | Circadian clocks and the regulation of hedonic appetite in mice

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**Introduction:** Unlimited access to calorie-dense, palatable food is a hallmark of Western societies and substantially contributes to the worldwide rise of metabolic disorders. In addition to promoting overconsumption, palatable diets dampen daily intake patterns, further augmenting metabolic disruption. Homeostatic and non-homeostatic aspects of appetite regulation are governed by distinct neuronal circuits.

**Objectives and aims:** Analyzing the role of different CNS tissue clocks in the regulation of appetite rhythms in mice.

**Methods:** We developed behavioral paradigms to analyze time effects on the regulation of homeostatic and non-homeostatic food intake behavior in mice.

**Results:** While homeostatic intake peaks in the active phase, conditioned place preference and choice experiments show an increased sensitivity to overeating on palatable food during the rest phase. This hedonic appetite rhythm is driven by endogenous circadian clocks in dopaminergic neurons of the ventral tegmental area (VTA). Mice with disrupted clock function in the VTAshow dampenedhedonic overconsumption rhythms without affecting homeostatic intake.

**Conclusions:** These findings assign a functional role of VTA clocks in modulating palatable feeding behaviors and identify a potential therapeutic route to counteract hyperphagy in an obesogenic environment.

**Disclosure**: No

## O220/P961 | Neurobiology of information processing during phasic and tonic rem sleep

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REM sleep is usually conceptualized as a homogeneous sleep state, despite its heterogeneous nature. Whereas NREM sleep oscillations and phasic events (e.g., spindles) are well studied and delineated in relation to sleep-related information processing activities, including learning and memory consolidation, the heterogeneous nature of REM sleep with its phasic and tonic constituents has been largely neglected so far, which may obscure its potential contributions. Systematically investigating the respective roles of tonic and phasic REM sub-states and their interaction with other states of vigilance to achieve efficient information and memory processing needs to be further developed. In this talk I will introduce the basic concepts and discuss how and to what extent REM tonic and phasic components support information processing in the sleeping brain.

**Disclosure**: No

## O047/P962 | Dim light in the evening delays circadian rhythms, sleep and cognitive performance

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In modern societies we are routinely exposed to artificial light, including the electric lighting in our homes as well as light-emitting electronic devices. Exposure to dim light in the evening has been shown

to increase our alertness before bedtime, delaying melatonin timing and sleep onset, and increases sleepiness the next morning. Using a mouse model of dim light in the evening (comparable to the light levels experienced by humans under electric lighting conditions), we show that these conditions delay circadian activity, sleep and body temperature. In addition, these conditions delay circadian rhythms in the brain and in organs throughout the body, including the heart, liver and adrenal gland. These effects persist in the absence of the blue-light sensitive circadian photoreceptor melanopsin. We go on to show that the normal rhythm of learning and memory performance is reversed, which may be related to changes in sleep/wake timing. This approach allows us to investigate the intensity and wavelength (colour) of artificial light during the day and in the evening to help avoid these disruptive effects, as well as allowing us to investigate whether long-term exposure to dim light in the evening has adverse health consequences.

**Disclosure**: No

## O061/P963 | Heart rate patterns during wakefulness and sleep to phenotype osa

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**Introduction:** Obstructive sleep apnea (OSA) is a sleep disorder with a high prevalence in the general population.

**Objectives:** One of the challenges is to correlate finding in polysomnography with brain dynamics which could be characteristic for OSA. One pathophysiological pathway may be through the autonomous nervous system. An outflow of the autonomous nervous system is heart rate. It is recognized that sleep apnea events during the night are accompanied by cyclical variation of heart rate. Regarding brain dynamics, heart rate increases with cortical arousal at the end of apnea events. However not only the changes of heart rate during sleep are characteristic for OSA, but we observe carry over effects on heart rate during quiet wakefulness.

**Methods:** For a systematic study we investigated 1247 heart rate patterns during wakefulness prior to sleep onset in subjects recruited for the Sleep Apnea Global Interdisciplinary Consortium (SAGIC). Five-minute ECG recordings were analyzed using time and frequency domain parameters as well as non-linear analysis parameters. Parameters were compared to OSA severity in terms of AHI.

**Results:** We found lower values in time domain and non-linear analysis parameters for more severe OSA. The complexity of heart rate variability decreased with an increase of AHI.

**Conclusions:** This may be a consequence of changes to the autonomic nervous system cause by OSA. Obese subjects with OSA showed a shirt towards sympathetic dominance. Taken together this may help in phenotyping OSA patients at risk for cardiovascular consequences.

**Disclosure**: No

## O130/P964 | Automatic detection of abnormal sleeping patterns in stroke patients using high-frequency sleep staging

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**Introduction:** Standard sleep staging methods compress polysomnographic data into 30 s sleep stages. Automatic scoring models, such as U-Sleep, make it possible to extract sleep stages at much higher frequencies. It has been hypothesized that such scores may be indicative of neurophysiological processes and may carry additional diagnostic information.

**Objectives:** To investigate if high-frequency outputs of the U-Sleep model contain additional diagnostic information for separating stroke patients from healthy and sleep-disordered controls compared to typical 1/30 Hz expert-derived sleep stages.

**Methods:** Overnight polysomnography (PSG) was performed for 20 healthy individuals, 39 patients undergoing diagnosis for sleep disorders and 233 stroke patients in the acute/sub-acute phase. Three human experts derived sleep stages at 1/30 Hz frequency, while the U-Sleep model was used to extract stages at 1/30, 1 and 12.8 Hz. Sleep stage transition-triplet frequencies were computed from expert- and automatically derived stages at each frequency. Cross-validation classification experiments using Random Forrest models were performed to separate stroke patients from healthy and sleep-disordered controls based on triplet frequency features. Classification performance was evaluated using the macro F1-score. Each experiment was repeated 50 times, and median performances obtained using automatic and expert scores were compared using two-sided Wilcoxon Signed Rank tests.

**Results:** U-Sleep performed sleep staging at 1/30 Hz with an F1-overlap to experts of 0.83 ± 0.18 for stage wake, 0.86 ± 0.15 for stage non-REM, and 0.64 ± 0.35 for stage REM (mean ± 1 STD, $N = 233$). Using expert derived stages, the classification experiments separated stroke patients from controls with macro F1-scores of 0.74 ± 0.01 (median ± 1 MAD, $N = 50$). In comparison, using U-Sleep scores resulted in lower classification performance at 1/30 Hz frequency (0.68 ± 0.02, $p < 0.001$), better performance at 1 Hz (0.76 ± 0.01, $p < 0.001$) and even higher performance at 12.8 Hz (0.80 ± 0.01, $p < 0.001$).

**Conclusions:** High-frequency sleep stage representations as output by the U-Sleep model are informative for separating stroke patients from healthy and sleep-disordered controls. Higher staging frequencies allowed for a better classification, ultimately exceeding that of human experts scores. Further work is needed to address if high-frequency U-Sleep scores reflect underlying neurophysiological processes or, for instance, model uncertainty on difficult cases.

**Disclosure**: No

## O223/P965 | How phasic and tonic rem sleep microstates modulate sleep disorders

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While it is well known that many sleep and neurological disorders are modulated by sleep stages, with a traditional dichotomy between rapid-eye-movement (REM) and non-REM (NREM) sleep, the pathophysiological relevance of the heterogeneous nature of REM sleep is an emergent issue. REM sleep microstates result from the involvement of distinct physiological networks, and are associated with different neurophysiological features and functional correlates; this translates into a distinct influence of phasic (pREM) and tonic (tREM) REM sleep on several conditions.

In the field of neurological disorders, epilepsy is probably the most closely related to sleep. The enhancing effect of NREM sleep on epileptic activity in generalized and focal epilepsy has been widely reported. On the contrary, REM sleep exerts a protective effect on seizures and interictal activity, including spikes and high frequency oscillations, by decreasing their density and spreading. This inhibitory effect is even more pronounced in pREM and may result from an increased cholinergic tone, leading to a higher desynchronization of cortical activity. Interestingly, the persistence of pathological ripples during pREM may have a localizing value for the seizure onset zone.

In the field of sleep disorders, the occurrence or expression of several conditions is modulated by REM sleep microstates. Among parasomnias, REM sleep behavior disorder is the most prominent example: complex behavioral and major motor events occur preferentially during pREM, which may be due to a stronger activation of the motor cortex in pREM than in tREM, as suggested by intracerebral recordings in patients with epilepsy. In narcolepsy type 1, phasic components of REM sleep are increased, including REMs density and phasic EMG activity. Regarding sleep-related motor disorders, data are scarce and conflicting, but some studies suggest that excessive fragmentary myoclonus and sleep-related head jerk might be exacerbated in pREM. In sleep-related breathing disorders, a particular vulnerability of ventilation has been demonstrated during pREM, associated with reduced genioglossus activity. In insomnia, pREM might be a state abnormally sensitive to sensory afferences. Thus, data from sleep disorders studies reinforce the relevance of the distinction between REM sleep microstates and provide new keys to the understanding and management of these disorders.

**Disclosure**: No

## O126/P966 | Modelling intra-individual variability in sleep timing

A. Phillips[1]
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**Introduction**: Irregular sleep/wake patterns have been associated with poor health outcomes. Computational models have become a powerful tool for understanding how physiological and environmental factors influence human sleep/wake patterns. However, most computational models of sleep have been deterministic, meaning they do not represent realistic intra-individual variation in sleep/wake patterns. We developed a new modeling approach to investigate the causes of intra-individual variability, and to study these factors in the context of antidepressant treatments.

**Objectives**:

(1) To investigate physiological and environmental factors that may contribute to irregular sleep/wake patterns using a computational model.

(2) To investigate these factors in the context of antidepressant treatments that may enhance light sensitivity.

**Methods**: A previously validated computational model was used to simulate weekly schedules, including a source of random intra-individual variation in sleep propensity. Daily light patterns were simulated, including typical levels of light exposure during the solar day and a fixed indoor light level during other waking hours (e.g., the evening after sunset). Sleep regularity was computed by applying the sleep regularity index (SRI) to the generated sleep/wake patterns. Simulated SRI was investigated as a function of work schedule, light levels, and light sensitivity.

**Results**: The model predicted realistic sleep/wake patterns, including day-to-day variation in sleep/wake timing within a typical range for SRI. Sleep/wake patterns were predicted to be less regular under conditions with greater variability in the timing in work/social constraints. Increasing the sensitivity of the model's circadian clock to light also resulted in less regular sleep/wake patterns, particularly under conditions with greater evening light levels, due to greater phase resetting by light.

**Conclusions:** Irregular sleep/wake patterns arise from a combination of environmental and physiological factors. Higher sensitivity of the circadian system to light is identified as a potential vulnerability to adopting irregular sleep/wake patterns, with this effect being enhanced if indoor evening light levels are too high. This should be considered in the context of antidepressant treatments that may enhance circadian light sensitivity.

**Disclosure**: Yes

**Conflict of Interest statement:** I have received research funding from Versalux and Delos. I am a co-founder and co-director of Circadian Health Innovations.

## O046/P967 | Effects of sleep-wake schedules on neurobehavioral performance: insights from biophysical modelling

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**Introduction:** Sleep is essential for clearance of metabolic byproducts from the brain, memory consolidation, and alertness. Optimal sleep

quality and quantity are achieved when sleep is aligned with the dip in the circadian drive, so daytime sleep as seen in shiftwork, jetlag, and napping is less restorative. Inadequate or mistimed sleep impairs neurobehavioral performance. While effects of acute sleep disturbances are explained well by existing mathematical models of performance, long-term dynamical changes as seen in aging or chronic sleep restriction are not well understood.

**Objectives**: Identify potential mechanisms responsible for changes of neurobehavioral performance in response to disturbed sleep-wake schedules at time scales from several days to decades.

**Methods**: Biophysical model of arousal dynamics was used to investigate the bi-directional relationships between behavioral sleep-wake schedules, accumulation of the total sleep drive, and neurobehavioral performance as measured using the psychomotor vigilance task (PVT). The model simulates the flip-flop switch between the sleep- and wake-active neuronal populations which is under control of the homeostatic and circadian oscillators and PVT lapses are predicted as a weighted sum of the circadian and homeostatic drives.

**Results**: Various scenarios of sleep-wake schedules were simulated and compared to experimental data for both group average and individuals. This included normal sleep, shiftwork, sleep restriction, and changes of sleep with aging. We found that a homeostatic drive incorporating both fast and slow time constants is required to reproduce both short-term and long-term changes in neurobehavioral performance at the same time. This indicates involvement of several metabolic byproducts in sleep homeostasis including, for example, adenosine for fast clearance and tau-protein and beta-amyloids for slow clearance. Introducing of obstruction of metabolite clearance over time, either due to chronic sleep debt, trauma, or otherwise disturbed clearance, predicted runaway of neurobehavioral performance above a critical threshold at timescales consistent with development of Alzheimer's disease.

**Conclusions**: Neurobehavioral performance in response to short-term and long-term disturbances in sleep-wake schedules is predicted to be regulated by multiple brain metabolites having a range of time scales: from several hours to several days.

**Disclosure**: No

## O128/P968 | Psychedelics in psychiatry – neurobiology and potential clinical applications

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Due to their unique effects on consciousness, psychedelics offer the opportunity to investigate the neuropharmacological mechanisms underlying alterations in perception and cognition important for increasing our understanding of psychiatric disorders. Furthermore, renewed interest in the potentially beneficial clinical effects of psychedelics warrants a better understanding of their underlying neuropharmacological mechanisms. However, major knowledge gaps remain regarding the neurobiology of psychedelics in humans.

In our studies, we show that LSD and psilocybin modulate brain connectivity and subjective effects via agonistic activity on the serotonin 2A receptor in humans. We additionally show that the neural correlates of psychedelic-induced states differ from non-pharmacologically induced altered states of consciousness. Furthermore, our studies in clinical populations are starting to elucidate the therapeutic mechanisms of action of psychedelic substances.

Our results thus attenuate major knowledge-gaps regarding the neurobiology and neuropharmacology of psychedelics. They therefore extend our knowledge on the pharmacological basis of cognitive and emotional processes and provide a scientific roadmap for the optimization of psychedelic-assisted treatment approaches.

**Disclosure**: No

## O222/P969 | Cortical and subcortical activations during phasic rem sleep: data from intracerebral recordings

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Different intracerebral EEG studies have shown that the distribution of brain activity during physiologic REM sleep in humans is not temporally and spatially homogeneous. Indeed, some brain regions shows a transient activation, especially concomitant with the occurrence of rapid eye movements (phasic REM sleep). Specifically, recordings with intracerebral electrodes sampling the human motor cortex in pharmacoresistant epileptic patients showed a pattern of electroencephalographic (EEG) activation during phasic REM sleep similar to that observed during the performance of a voluntary movement during wakefulness. This pattern was absent during tonic REM sleep (resembling relaxed wakefulness) and other frontal areas, such as dorsolateral prefrontal cortex. It can be hypothesized that this activation is specific of primary brain areas and not of the associative ones. Other studies revealed increased amygdala activation in a close time relation to the rapid eye movements of REM sleep, suggesting its central role for a further limbic–paralimbic network activation during this sleep substate. Finally, the analysis of single-unit activities and intracranial electroencephalography across the human medial temporal lobe and neocortex showed that rapid eye movements during sleep were associated with transient bi-phasic modulations of spiking activity in the mid temporal lobe, related to evoked potentials in depth EEG signals, suggesting a transient increase of cortical excitability during REM sleep.

A recent wok analyzing the electric activity patterns of the anterior nuclei of the thalamus and their functional connectivity with scalp EEG revealed an increased thalamocortical synchronization in phasic compared with tonic REM, showing that the heterogeneity of REM sleep microstates is not limited to cortical activity but also involved subcortical structures and thalamocortical networks.

This finding may help clarify cortical contributions to certain phenomenological aspects observed in REM sleep behavior disorder (RBD).

The observation that local activations and variations in cortical background rhythms occur in REM sleep argue in favour of an active role of the cortical motor areas in the genesis of RBD manifestations. An articulated model keeping into account both cortical networks and brainstem motor regulators can be hypothesized.

**Disclosure**: No

## O136/P970 | Sex matters when diagnosing and treating rls patients

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The available epidemiological studies clearly indicate a significant female prevalence of restless legs syndrome (RLS) in adults which is not usually seen in children or teenagers. Many studies suggest a possible sex difference in the phenotypical presentation of RLS, manifesting with predominantly sensory symptoms in women and predominantly motor symptoms in men. Women could report symptoms at a lower severity level compared with men complaining of worsening severity and frequency of RLS symptoms over time. Females more often present with sleep onset difficulties or frequent awakenings at night. Quality of life is considerably impaired by RLS, but these impairments, in contrast to many other disorders, seem similar both in males and females, although more studies on this issue are needed. In addition, women with RLS have a higher risk of hypertension than those without RLS, independent of several known risk factors for hypertension. Possible explanations for the RLS prevalence in females include pregnancy, sex hormones and iron status. Surprisingly, RLS prevalence increases with age, including post-menopausal women, and estrogen replacement therapy has no clear effect. These data question a causative role of estrogens, but this might also be masked in elderly women by other yet unknown effects of ageing. To further elucidate the peculiarities of female RLS, controlled longitudinal studies are needed. Understanding the possible different mechanisms that underlie RLS both in males and females could lead to new treatment options and could guide future functional research.

**Disclosure**: No

## O050/P971 | The effect of light on sleep and sleepiness in the real world

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Light has a ubiquitous and potent effect on daily (24 h) rhythms in physiology and behaviour. This is because these rhythms are synchronized through the sensitivity of the circadian pacemaker to the light. As a result, light exposure at an inappropriate time leads to a disruption of circadian rhythms and sleep, something we experience in our daily lives. In particular, the artificial light we are exposed to in the evening delays sleep onset, not only because it prolongs our engagement in visual activities but also because light suppresses hormone melatonin delaying its nocturnal rise. This non-visual effect of light is mediated by a multi-component photoreceptive system with unique wavelength, intensity and spectral characteristics. Our quantification of this effect rests primarily on findings from controlled laboratory studies. This knowledge forms the bedrock for light based interventions in various work and clinical settings. Yet real-life is compounded by numerous biopsychosocial factors that modulate the non-visual effects of light on physiology and behaviour and field studies are few. In this talk, I will focus on findings from observational studies on the effects of ambient light exposure in ecological settings, highlighting potential confounding factors.

**Disclosure**: No

## O045/P972 | Impact of daytime napping on circadian markers, cognition and brain integrity in the aged

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**Introduction:** Sleep homeostasis and circadian rhythmicity can act as powerful modulators of human brain function. During ageing, cognitive decline goes along with altered sleep regulation. One visible manifestation of such alteration might be the increasing occurrence of chronic daytime napping while getting older. Here we assessed the impact of napping on circadian sleep propensity, cognition and its underlying structural and functional brain changes in healthy older adults.

**Methods:** Fifty-six healthy older adults were prospectively recruited with respect to their napping habits (20 women/69+−5.5 y., ½ nappers). All individuals underwent actimetry screening to objectify daytime rest frequency, timing and duration. They further underwent a 40-h multiple nap constant routine (10 alternating cycles of 80 min of sleep opportunity and 160 min of scheduled wakefulness). During the protocol, salivary melatonin, subjective sleepiness, psychomotor vigilance and electrophysiologically derived sleep parameters over nap opportunities were assessed. Participants finally underwent functional and structural magnetic resonance imaging (MRI). During functional MRI, they performed a working memory task (Sternberg paradigm) allowing for the assessment of functional compensation with increasing working memory load.

**Results:** Compared to non-nappers, nappers presented a reduced amplitude of circadian sleep propensity, characterized by higher sleep efficiencies during daytime sleep opportunities and lower sleep

efficiency during night time sleep (interaction session*group: $p < 0.05$). Furthermore, nappers showed reduced episodic memory performance compared to non-nappers ($p < 0.05$) and more particularly daytime rest frequency was negatively associated with memory performance ($p < 0.05$). Finally, independent of nap group, actimetry-derived late daytime rest timing was associated circadian misalignment as expressed by an increased phase angle of entrainment between dim light melatonin onset and activity onset time ($p < 0.05$).

**Conclusion:** Our results suggest altered circadian sleep regulation and associated reduced cognitive performance in healthy older nappers. They are in line with recent reports suggesting chronic and long daytime napping as a health risk factor in the aged, including for cognitive fitness. The assessment of daytime napping and associated circadian sleep propensity on functional compensation during working memory performance as well as on structural brain integrity (magnetization transfer derived myelin estimation) is currently ongoing.

**Disclosure**: No

## O122/P973 | The role of mch and ambient temperature on rem sleep and cataplexy expression in narcolepsy

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**Introduction:** The lateral hypothalamic melanin-concentrating hormone (MCH) neurons play a regulatory role in REM sleep, including their ability to dynamically increase REM sleep expression during thermoneutral ambient temperature (Ta) warming (Komagata et al., 2019). Moreover, our prior data have shown that thermoneutral Ta warming increases REM sleep but decreases cataplexy in narcoleptic hypocretin knock-out (Hcrt-KO) mice.

**Objectives:** Given the reciprical (indirect vs direct) inhibition between the Hcrt and MCH systems, we hypothesize that loss of Hcrt may disinhibit MCH activity resulting in the increased REM sleep propensity characteristic of narcolepsy, whereas periods of low MCH activity may exacerbate boundary state instability and favor cataplexy.

**Methods:** Using fiber photometry calcium imaging, we first investigated the normal dynamics of MCH activity across the sleep-wake cycle in MCH: ce mice at both constant Ta and thermoneutral Ta warming. We then evaluated the role of the MCH system in the expression of REM sleep and cataplexy in MCH: cre/HcrtKO narcoleptic mice. In a separate set of experiments, we then silenced MCH neuronal activity using the ArchT opsin during four 30-min sessions at two-hour intervals during the dark phase in MCH: cre/HcrtKO mice.

**Results:** During the light and dark phases, fiber photometry revealed that MCH-dependent signal markedly increased in anticipation and during REM sleep but dropped during NREM sleep and wake states in both animal models. MCH:cre/HcrtKO mice showed increased REM sleep expression during the dark phase during the Ta warming condition. However, cataplexy expression was significantly decreased during Ta warming. MCH activity in narcoleptic mice showed dynamic modulation in anticipation of REM sleep but remained silent prior to cataplexy onset, even though MCH activity then increased during cataplexy. MCH activity decreased from REM sleep or cataplexy to the wake state. Finally, optogenetic inhibition of MCH neurons in MCH: cre/HcrtKO mice significantly increased cataplexy expression.

**Conclusion:** Although MCH activity increases during both REM sleep and cataplexy, increased MCH activity anticipates REM sleep onset whereas MCH inactivity or silencing anticipates/promotes cataplexy. These data are consistent with our hypothesis that increased MCH activity in narcolepsy may drive increased REM sleep propensity, whereas low MCH activity favors cataplexy onset and state instability.

**Disclosure**: No

## O064/P974 | Integration of genetic information into clinical practice for rls - are we there yet?

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Over the past years, genome-wide association studies have identified more than 20 individual genetic risk variants for RLS. While they attest the important role of genetics in shaping disease susceptibility, they account for only 20% of the heritability of RLS. Therefore, more genetic risk factors remain to be discovered. Nevertheless, polygenic risk scores can be constructed from the currently available data. These scores allow identification of individuals with high load of genetic risk factors for RLS, but the prediction accuracy is still low. Integration of additional genetic and non-genetic risk factors will be key for translation into patient care. Besides prediction of disease risk, genetic scores may also be used to stratify patients for treatment or prevention approaches. Large cohorts of extensively and carefully phenotyped RLS patients are needed to evaluate potential stratification schemes.

**Disclosure**: Yes

**Conflict of Interest statement:** I have filed a patent application.

## O226/P975 | Calcium activity in dendrites: relation to sleep oscillations

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Sleep is important for brain plasticity during development and adulthood but how sleep oscillations, known to be important for cognitive function, contribute to this process is unknown.

Structural and functional changes within apical dendrites of layer 5 (L5) neurons in the cortex have been shown to support experience-dependent plasticity during sleep[1]. Using *in vivo* calcium ($Ca^{2+}$) imaging in rodents, we have previously shown that $Ca^{2+}$ activity of populations of L5 apical dendrites is increased and synchronized during non-rapid eye movement (NREM) sleep spindle (sigma: 9–16 Hz) oscillations[2]. But how experience modifies the spindles/dendritic $Ca^{2+}$ coupling during sleep remained to be explored.

We address this question by investigating how sleep and experience influence $Ca^{2+}$ activity in L5 apical tuft dendrites using two-photon imaging. We also investigated $Ca^{2+}$ changes in L5 cell bodies for comparison. Given the pivotal role of precisely timed dendritic inhibition in plasticity, we also imaged somatostatin (SST) interneurons that are known to target apical dendrites. To assess the influence of experience, we compared $Ca^{2+}$ activity during a baseline period and after three hours of exposure to an enriched environment. The dynamics of $Ca^{2+}$ activity was assessed in relation to EEG oscillations in the same animals.

Our current results confirm that modulation of $Ca^{2+}$ activity in the apical tuft dendrites during NREM sleep is decoupled from the cell body, as previously suggested for the apical trunk dendrites[2]. Furthermore, correlation analysis shows a reverse relation between NREM EEG oscillations with calcium activity in dendrites and SST neurons. Enriched environment exposure affects primarily the link between sigma power and $Ca^{2+}$ activity in both dendrites and SST neurons. Our current results support a model in which spindle oscillations specifically influence the circuits regulating dendritic activity during sleep.

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**Disclosure**: No

## O063/P976 | How can animal models accelerate rls research?

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Animal models have the potential to accelerate the mechanistic understanding of the pathophysiology of human diseases and the development of novel and effective therapies. Careful evaluation of validity criteria, and particularly of face, construct, and predictive validity, is paramount for animal models of human disease in general. This is particularly relevant to the development of animal models of the Restless Legs Syndrome (RLS), which is challenging because RLS diagnosis is based on subjective symptoms and RLS etiology is still unclear. In the context of RLS animal models, face validity indicates how closely the model reproduces the RLS clinical features. Construct validity reflects how well the mechanisms used to induce the RLS clinical features in the model reflect the currently understood RLS pathophysiology. Predictive validity indicates how well the animal model allows translation of results such as drug screening or development to patients. Consensus guidelines on the face validity of rodent models of RLS have been recently published (DOI: 10.1002/mds.28401) by a task force of the International Restless Legs Syndrome Study Group (IRLSSG). These guidelines focused on activity monitoring to detect and quantify the expected objective consequences for rodent behavior of the subjective sensory limb discomfort, urge to move, and relief with movement, which correspond to essential diagnostic criteria for RLS. The day-night and circadian pattern of activity alterations was taken into account to translate the criterion that symptoms only occur or are worse in the evening or night. Evaluation of sleep disturbances and limb movements during sleep with video-polysomnography was recommended to translate the corresponding objective clinical features that impact RLS diagnostic assessment or support RLS diagnosis. Pharmacological challenges, such as with dopamine receptor antagonists or agonists, or with iron deficiency or supplementation, were recommended to elicit/aggravate or rescue the pathological phenotype, thereby also demonstrating that such phenotype is not solely primary to another medical or behavioral condition. These guidelines need to be extended to invertebrate and non-human primate models and expanded to consider construct and predictive validity. Nevertheless, they may represent an important step towards acceleration of RLS research by means of animal models.

**Disclosure**: No

## O059/P977 | Challenges in non-invasive ventilation (niv)

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There are a range of long term and emerging challenges in non-invasive respiratory support.

Acute challenges have always been posed by the management of acute hypoxaemic respiratory failure, and these were highlighted during the height of the covid pandemic. Randomised controlled trials have helped clarify the role of CPAP/NIV versus highflow nasal oxygen (HFNO) therapy, the risks of aerosol generation, and sequential application.

For long term management of nocturnal hypoventilation in obesity hypoventilation syndrome the appropriate timing and use of CPAP and NIV is now evidence based and further work will help illuminate

the roles of CPAP and NIV in patients with COPD-OSA overlap syndrome, and the titration of therapy. Long term outcomes of home NIV in COPD are becoming clearer.

Long term NIV has proved lifesaving in patients with neuromuscular disorders. New therapies for children and young people with inherited neuromuscular disease such as spinal muscular atrophy, Duchenne muscular dystrophy and myotubular myopathy make the integration of respiratory support more challenging, and new guidance on this of rapidly evolving area is now available.

**Disclosure**: No

## O221/P978 | Phasic and tonic rem microstates in the service of sleep stability and environmental monitoring

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**Introduction:** Rapid-eye-movement (REM) sleep is a fundamental neural state that plays critical roles in a variety of functions spanning from basic physiological mechanisms to highly complex cognitive processes such as learning and memory. Although our knowledge regarding the complex neural circuitry that orchestrates REM sleep increased substantially in the last decade, the functions and mechanisms of this intriguing neural state remain rather elusive. Although REM sleep is considered to be a homogeneous sleep state, it is characterized by the alternation of two remarkably different microstates: phasic and tonic REM showing differences in arousability, sensory processing, as well as in the activity patterns, and functional synchronization of spontaneous cortical oscillations.

**Objectives:** In this talk, I will present two studies that discuss the differences across phasic and tonic microstates with respect to event-related cortical activity (heart-beat evoked potentials), and thalamocortical synchronization based on sleep EEG, and intrathalamic recordings of human REM sleep.

**Aims:** (1) to investigate interoceptive processing as quantified by the heartbeat evoked potential (HEP) during REM microstates. (2) to examine electric activity patterns of the anterior nuclei of the thalamus as well as their functional connectivity with scalp EEG recordings during REM microstates and wakefulness.

**Methods:** (1) We contrasted the HEPs of phasic and tonic REM periods using two separate databases that included the nighttime polysomnographic recordings of healthy young individuals ($N = 20$ and $N = 19$). (2) Local field potentials of the anterior thalamus and functional synchronization between the thalamus and scalp EEG were examined in in a group of epilepsy patients ($N = 12$, 7 females).

**Results:** (1) We find a differential HEP modulation of a late HEP component (after 500 ms post-R-peak) between tonic and phasic REM. (2) Anterothalamic local field potentials (LFPs) showed increased high-alpha and beta frequency power in tonic compared with phasic REM. We observed increased thalamocortical synchronization in phasic compared with tonic REM sleep, in the slow and fast frequency ranges.

Conclusions: A distinctive approach to phasic and tonic REM microstates may shed new light on the mechanisms and functions of REM sleep, as well as on the dysfunctional patterns observed in pathological conditions affecting REM sleep.

**Disclosure**: No

## O127/P979 | What determines sleep and circadian timing in humans in the field?

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**Introduction:** Sleep timing depends on family and work constraints, biologically preferred sleep timing, environmental light exposure and temperature, stimulants such as caffeine, and mental health.

**Objectives:** Our overall aim is to understand the relative contribution of different physiological, environmental and societal factors in determining sleep phenotypes, with the objective of designing interventions for those whose sleep is misaligned with their circadian clock and providing further support to policy recommendations on the light environment.

**Methods and Results:** Our approach is to combine data with quantitative, physiologically-informed mathematical models to test hypotheses on mechanisms and provide quantitative predictions. The mathematical models incorporate sleep homeostasis, circadian rhythmicity, the interaction of the biological clock with the light environment and allow for the fact that we can override the physiological cues to sleep. At the population level, such models explain how chronotype depends on individual physiological factors such as intrinsic circadian period and on light exposure and capture observed changes in sleep timing across time zones. These mathematical models provide plausible hypotheses to explain changes in sleep duration and timing across the lifespan, and highlight that greater sensitivity of adolescents to light exposure patterns can be explained by observed changes in sleep homeostasis. At the individual level, personalised models that take longitudinal light data and match sleep duration and timing have been created and have provided a parsimonious explanation seasonal desynchrony with the 24 h day, as seen in some people. Here, we will review recent work and outline current challenges, drawing on data on day-to-day variability in sleep timing and sleepiness in a population of 19 students in which data were collected for three weeks in the late autumn (standard time) and again in the late spring (daylight saving time).

**Conclusions:** Quantitative mathematical models based on physiology can provide mechanistic insight. Such models can help understand the relative contribution of physiological, behavioural and environmental factors and contribute to policy debates. Combining such models with longitudinal data holds promise for the design of personalised low-burden and low-cost interventions. However, challenges remain in

modelling sleep quality, day-to-day variability and subjective and objective measures of performance.

**Disclosure**: Yes

**Conflict of Interest statement:** Anne Skeldon has worked a consultant for Transport for London and to F. Hoffmann-La Roche Ltd.

## O117/P980 | How sleep consolidates rewarded experiences in adults and in children?

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Sleep spontaneously reactivates memory traces. Because rewarded experiences are better remembered than neural ones at wake, we hypothesis that sleep selects and favors the consolidation of these events. Using functional MRI and a brain decoding approach, we showed that patterns of brain activity observed during waking behavior spontaneously reemerge during slow-wave sleep. Critically, we reported a privileged reactivation of neural patterns previously associated with a rewarded task (i.e., winning at a complex game). Next, we recorded EEG signal in emotional brain regions using intracranial electrodes placed in medically resistant epileptic patients. During wakefulness, we presented the patients with rewarding pictures paired with a sound. Then, we tested for the reinstatement of reward-associations by delivering the sound during a subsequent period of sleep. We found that the reactivation of reward memories during sleep enhanced slow-oscillation and spindle activity in the orbitofrontal cortex, paralleled with an increase in theta connectivity between the hippocampus and the orbitofrontal cortex. Finally, we measured sleep architecture in children from 6 to 12 years-old, after they encoded rewarded and neutral stimuli. While sleep duration and the proportion of each sleep stage do not affect the consolidation of rewarded items, we observed that delta power was significantly correlated with emotional memory performances. Taken together, these data demonstrate that sleep offers a particular state of consciousness favorable to the spontaneous reactivation and the processing of rewarded events both in adults and in children.

**Disclosure**: No

## O124/P981 | Narcolepsy with cataplexy is caused by epigenetic silencing of hypocretin neurons

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Narcolepsy with cataplexy is a sleep disorder believed to result from autoimmune destruction of hypocretin (HCRT) neurons. We show that HCRT cells co-express the neuropeptide QRFP, and HCRTcell-ablated mice lose *Qrfp* expression, while *Hcrt*gene-ablated mice do not. Similar to *Hcrt*-KO mice, narcolepsy post-mortem samples show intact *QRFP* expression, suggesting the presence of HCRT neurons. We show that a CpG residue in a phylogenetically conserved, functional motif of the *HCRT* promoter binds ETS1:PAX5 in a methylation-sensitive manner and shows selective hypermethylation in patients' hypothalamus. Disruption of*Ets1* or *Ets1-Pax5* in mice and zebrafish causes impaired *Hcrt* expression. As HCRT cells, CRH neurons are lost in narcolepsy and we show that the *CRH* promoter is also hypermethylated at a critical CRE-binding site in patients. Our results suggest that HCRT and CRH neurons are epigenetically silenced in narcolepsy patients, questioning the auto immunity hypothesis, and opening the possibility to reverse or cure narcolepsy.

**Disclosure**: No

## O120/P982 | A need for worldwide collaboration in neuroimaging/genetics of sleep research: The enigma-sleep framework

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Recent neuroimaging and genetic evidence have advanced our understanding of the neurobiological mechanism of sleep physiology, sleep disorders and the interplay between sleep and neuropsychiatric disorders. However, most conventional individual studies have limitations in identifying reproducible effects due to their small sample sizes, genetic variability, heterogeneous clinical characteristics, and divergent imaging acquisition, preprocessing and analytic methods. Thus, a need for a consensus multi-centre effort in sleep research is inevitable to increase the number of samples, and harmonize the methods of data preprocessing and analysis using the pre-registered unified protocols. Recently, the ENIGMA-Sleep consortium has been launched with the collaboration of around 100 scientists across 15 countries to perform large-scale worldwide neuroimaging and genetics studies in the sleep field. The ENIGMA-Sleep group adopts a 'bottom-up' approach, whereby the interested researchers can join and suggest/guide a project, rather than just contributing to some predetermined set of analyses by sharing data. Currently, there are several ongoing projects about neural correlates of insomnia disorder using structural brain data, the predictive role of sleep on cognitive performance among population-based samples, predicting brain age gap following sleep deprivation, and transdiagnostic neural correlates of sleep across mental illnesses.

**Disclosure**: No

## O216/P983 | Effect of psychiatric disorders and their treatment on sleep, somnolence and driving performance

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**Introduction:** Psychiatric disorders and their treatment seem to impair cognitive and psychomotor dysfunction, and, thus, may have an impact on driving performance.
**Objectives:** To review the existing literature on the effect of psychiatric disorders and their treatment on driving performance.
**Methods:** A literature search was performed on the PubMed database, using terms «psychiatric disorders AND driving performance», and "(psychiatric disorders OR schizophrenia OR depression OR OCD OR drugs OR alcohol) AND accident risk". Studies that were considered relevant, based on their title and abstract, were assessed with respect to inclusion in the literature review. A total of 77 studies were reviewed in detail and 53 of these were included.
**Results:** Psychiatric disorders were found to be related to increased risk of road traffic accidents (RTA). Depression correlated with high risk of RTA, although it seemed that this risk is minor when depression is treated. At the start of or when changing the antidepressant treatment the risk of RTA was higher. About a quarter of patients with schizophrenia were characterized as unfit to drive in one study; driving ability improved with treatment, especially with atypical antipsychotics. The diagnosis of bipolar disorder increased 1.66-fold the risk of RTA. Obsessive-compulsive disorder (OCD) increased the risk of serious RTAs, especially in women. Sleep duration was found to be shorter in OCD; various sleep-related disorders, especially excessive daytime sleepiness, were also correlated to high risk of RTA. Use of drugs while driving seemed to increase the risk of fatal and serious injury accidents: Statistically significant associations between drug use and involvement in RTAs were found for benzodiazepines, z-hypnotics and antidepressants. Alcohol was the most frequently identified psychoactive substance in the blood of drivers killed in RTA.
**Conclusions:** The results of this review show that psychiatric disorders do affect the incidence of RTA. Although pharmacological treatment may improve patient functioning, certain drugs and psychoactive substances can constitute a problem in traffic safety.
**Disclosure**: No

## O218/P984 | Sleep microstructure and early alzheimer's disease neuropathology

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Alterations in sleep are hallmarks of the ageing process and emerge as risk factors for Alzheimer's disease (AD). While the fine-tuned coalescence of sleep microstructure elements may influence age-related cognitive trajectories, its association with AD-related processes is not fully established. Here, we investigated whether key elements of sleep microstructure are associated with early amyloid-beta (A$\beta$) brain burden, hallmark of AD neuropathology, and cognition in 100 late-midlife healthy individuals (50–70 y; 68 women).

We first found that spontaneous arousal during sleep are heterogenous and differently associated with A$\beta$ and cognition. While the density of arousals associated with changes in sleep stages were associated with more early deposit of A$\beta$, the density arousals not interrupting sleep continuity were associated with less A$\beta$ burden and better cognitive performance to attentional tasks and with change in memory performance at 2 years. We further found the young-like co-occurrence of spindles and slow-depolarisation slow waves was associated to lower early burden of A$\beta$ and was predictive of memory decline at 2-year follow-up. In contrast the density of spindles and slow waves as well as other more macroscopic metrics of sleep were not associated with early deposit of A$\beta$.
These findings unravel early links between sleep, AD-related processes and cognition and support that the spontaneous arousals and the altered coupling of sleep microstructure elements that are key to its mnesic functions contributes to poorer brain and cognitive trajectories in ageing.
Support: ULiège, Wallonia-Brussels Federation, Fonds de la Recherche Scientifique (FNRS Belgium), Fondation Recherche Alzheimer (SOA-FRA Belgium), Fondation Léon Fredericq, EU FEDER programme
**Disclosure**: No

## O196/P985 | Mistimed dna repair in night work schedule

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**Introduction:** Circadian misalignment due to night shift work is associated with increased cancer risk. We investigated the potential role of disruption of the circadian transcriptome of hallmark cancer pathway genes.
**Methods:** $N = 14$ healthy human adults (aged 22–34; 10 males, 4 females) participated in a 7-day (6-night) laboratory study. Subjects were exposed to 3 days of either a simulated night shift schedule ($n = 7$) with daytime sleep opportunities (10:00 a.m.–6:00 p.m.) – or a

simulated day shift schedule ($n = 7$) with nighttime sleep opportunities (10:00 p.m.–6:00 a.m.). Subsequently, subjects underwent a 24 h constant routine protocol with blood sampling at 3 h intervals. From the blood samples collected during the constant routine protocol, lymphocytes were harvested and used for investigation. Here we analyzed the circadian rhythms of 726 mRNA targets from the NanoString PanCancer Pathway Panel and 17 core clock genes. Furthermore, we performed *ex vivo* functional assessments of sensitivity to endogenous DNA damage as well as exogenous DNA damage from ionizing radiation.

**Results:** Cosinor analyses showed that the simulated night shift schedule, as compared to the simulated day shift schedule, caused widespread disruption of circadian rhythmicity in core clock genes and among 13 hallmark cancer pathways. There was a marked difference in circadian rhythmicity in transcripts of the DNA repair pathway, which was significantly enriched ($p < 0.05$) for genes exhibiting circadian rhythmicity after the simulated day shift schedule, but not after the simulated night shift schedule. Endogenous DNA damage as assessed with alkaline comet assay was increased ($p < 0.001$) and the percentage of cells with DNA damage biomarker foci (BRCA1 and γH2AX) was higher ($p < 0.01$) after the simulated night shift schedule. Evening exposure to ionizing radiation (2.5Gy) caused a significant increase in DNA damage biomarker foci ($p < 0.05$).

**Conclusions:** We observed circadian transcriptome evidence of mistimed DNA repair mechanisms and molecular evidence of increased sensitivity to DNA damage in lymphocytes collected under constant routine after 3 days of a simulated night shift schedule. Thus, a night shift schedule may be associated with increased genomic instability, which may lead to elevated cancer risk in night shift workers.

*Supported by NIH R01ES030113, R21CA227381; CDMRP W81XWH-18-1-0100; and PNNL BRAVE under DOE DE-AC05-76RL01830.*

**Disclosure**: No

## O129/P986 | Representations of temporal sleep dynamics: an overview

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Sleep is characterized by an intricate variation of brain activity over time. Measuring these temporal sleep dynamics is relevant for elucidating healthy and pathological sleep mechanisms. In standard clinical practice, raw sleep signals are represented by 30 s sleep stages, which possibly do not reflect all relevant changes in sleep characteristics over the course of the night. Alternative representations may be better at capturing the temporal dynamics of sleep. Recently, the data science community has made a rapid shift from "conventional" human-defined representations to so-called data-driven representations learned by a machine. Additionally, besides the traditional PSG, many alternative measuring techniques based on wearables are emerging. The rapidly increasing possibilities for obtaining and processing sleep registrations have led to an abundance of data, which can be challenging to analyze and interpret. A structured overview of approaches to represent temporal sleep dynamics is presented, categorized based on the way the source data is compressed ranging from human-defined to machine learned. Most representations have been developed for in use in a specific context or application. Each category of representations has advantages and disadvantages. Standard human-defined 30-s sleep stages have the advantages of standardization and interpretability. Alternative human-defined representations are less standardized but offer a higher temporal resolution (in case of microstructural events such as sleep spindles), or reflect non-categorical information (for example spectral power analysis). Machine-learned representations offer additional possibilities: automated sleep stages are useful for handling large quantities of data, while alternative sleep stages obtained from clustering data-driven features could aid finding new patterns and new possible clinical interpretations. While newly developed sleep representations may offer relevant insights, they can be difficult to interpret in for example a clinical context. Therefore, there should always be a balance between developing these sophisticated sleep analysis techniques and maintaining clinical explainability.

**Disclosure**: No

## O053/P987 | Sleeping on it: Ditching or deepening distress?

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Sleep is an active state during which the brain reorganizes the synaptic connections between neurons, supporting consolidation and adaptation of memories and skills. The vast majority of studies and integrative reviews focused on sleep-related adaptation of skills and of memories for facts. Scholars of sleep and memory seldom consider that the sleep-facilitated synaptic plasticity processes also alter limbic, autonomic and behavioral responses embedded in the memory traces of distressing experiences. Even less considered is that the success of these processes determines the severity of emotional distress experienced with subsequent encounters with either reoccurring identical stimuli and contexts or resembling stimuli and contexts.

Sleep thus play a key role in emotion regulation. However, scholars studying emotion regulation limit their evaluations to the time scale of min and don't usually consider that emotion regulation processes could critically continue overnight. This presentation aims to bridge the gap between knowledge on sleep-related plasticity and knowledge on emotion regulation. Addressing emotion regulation in the context of sleep-related plasticity, unveils mechanisms underlying the long-standing epidemiological findings that disrupted sleep is key to the risk, severity and relapse of the most prevalent psychiatric disorders. Sound sleep is conductive to overnight desensitization to subsequent encounters with reoccurring identical distressful stimuli and contexts or resembling stimuli and contexts. However, restless sleep in its worst appearance may in fact even become maladaptive and

instead sensitize the limbic system to show an enhanced response to reoccurring identical distressful stimuli and contexts or resembling stimuli and contexts. These insights emerge by integrating three operational levels of brain function: experience and behaviour; physiological activity in neuronal circuits; and cellular, synaptic and molecular adaptations.

**Disclosure**: No

## O224/P988 | Astrocytes, ionostasis and sleep regulation

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Sleep is a universal biological phenomenon, which exists in the absolute majority of multicellular species across multiple taxa; even the most primitive cnidarian *Hydra vulgaris* with it diffuse nervous system falls asleep sleep. Transition between awake and sleep state are associated with complex changes in astroglia. About 1.4% of transcripts in forebrain astrocytes change during wake-sleep transition with 396 unique genes associated with wakefulness and 55 with sleep (Bellesi, 2015 #371). In parallel sleep affects morphology of astrocytic branches and perisynaptic leaflets. During sleep astrocytic perisynaptic processes retreat thus increasing extracellular volume and permitting facilitating neurotransmitter spillover; in contrast in awake state astrocytic synaptic coverage increases and tightens. Arousal emerges from release of neurotransmitters, which changes ionic composition of the brain fluids thus leading to a global increase in neuronal excitability and neuronal activity. In particular, arousal is associated with secretion of monoamines, associated with an increase in interstitial concentration of $K^+$ and with a decrease in concentration of $Ca^{2+}$, $Mg^{2+}$, and $H^+$, together with shrinkage of the interstitial space. Astrocytes, the key homeostatic cells of the CNS, are primarily responsible for controlling the ionic composition of the CNS fluids providing for the nervous tissue "ionostasis". which is directly involved in regulation of sleep behaviour.

**Disclosure**: No

## O121/P989 | Phenotyping chronic insomnia based on objective sleep measures: Diagnostic and treatment implications

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Over the last 40 years various classification systems have proposed insomnia subtypes on the basis of clinical and polysomnographic features (e.g., psychophysiological or paradoxical). However, these subtypes were not associated with satisfactory reliability and validity and new nosologies include only one diagnosis for chronic insomnia disorder (CID), which improved reliability and validity without promoting personalized treatments for the disorder. Hyperarousal has been suggested as a key feature of CID since the 60's. More recently, it has been proposed that physiologic hyperarousal is primarily present in insomnia with objective short sleep duration (ISSD) but not in those with objective normal sleep duration (INSD), forming the basis for phenotyping based on objective measures. The association of insomnia with mental disorders that is, depression has been shown since the 70's to be a key characteristic of the disorder. It is only in the last two decades that investigators have explored the association of insomnia with cardio metabolic health. After some reports in the 2000's suggesting that insomnia does not impact physical health, several research groups have reported that ISSD is associated with cardio metabolic morbidity. Given the association of insomnia with mental disorders, psychotherapy became the main stay treatment of insomnia in the US in the 60's/70s. In the 1990's, pioneers in psychological insomnia treatment such as Charles Morin and Jack Edinger proposed a systematic cognitive-behavioral treatment (CBT-I) which is now recommended as the "first-line" treatment. However nearly half of patients do not remit, and many others do not have access or interest in this treatment. Consequently, millions of prescriptions for "z-drugs" and benzodiazepines are written each year. Persistent concerns about the short-and long-term side effects of these drugs have led many practitioners to use other classes of drugs such as low dose heterocyclic "antidepressant" medications that is, trazodone, doxepin and mirtazapine. Retrospective analyses have shown that CBT-I is more effective in the INSD vs ISSD phenotype whereas preliminary studies indicate that low dose antidepressants are more effective in the ISSD phenotype compared to CBT-I. Prospective, large randomized clinical trials are needed to determine whether sleep medications and CBT-I have differential efficacy to the proposed insomnia phenotypes.

**Disclosure**: No

## O056/P990 | Circuit mechanisms underlying the ultradian regulation of rem sleep

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**Introduction:** A salient feature of mammalian sleep is the alternation between rapid eye movement (REM) and non-REM (NREM) sleep. However, the neural mechanisms that underlie the timing and duration of REM sleep episodes are still largely unknown.

**Objectives:** Our main objective was to first identify statistical factors underlying the timing and duration of REM sleep episodes in mice. Second, we aimed to provide further experimental support for our statistical findings by manipulating and recording the activity of REM sleep-promoting neurons in the dorsomedial medulla (dmM).

**Methods:** We recorded spontaneous sleep in mice and analyzed the resulting hypnograms and electroencephalogram (EEG) signals to identify factors in the sleep pattern and the spectral features of the EEG that are correlated with the timing and duration of REM sleep episodes. In addition, we performed and analyzed optogenetic stimulation experiments and in vivo recordings using fiber photometry of

REM sleep-promoting dmM neurons to provide experimental support for our statistical findings.

**Results:** Statistical analysis of spontaneous sleep in mice suggests the existence of two different types of sleep cycles: Short cycles form closely interspaced sequences of REM sleep episodes, whereas during long cycles, REM sleep is first followed by an interval of NREM sleep during which transitions to REM sleep are extremely unlikely. This refractory period is characterized by low power in the theta and sigma ranges of the EEG, low spindle rate and frequent microarousals, and its duration proportionally increases with the preceding REM sleep duration. Using our model, we estimated the propensity for REM sleep at the transition from NREM to REM sleep and found that entering REM sleep with higher propensity resulted in longer REM sleep episodes with reduced EEG power. Finally, we discuss experimental evidence derived from optogenetic stimulation experiments and in vivo recordings of inhibitory dmM neurons supporting these statistical findings.

**Conclusions:** Collectively, our results support the existence of a refractory period during which transitions to REM sleep are unlikely and a homeostatic process operating on the ultradian time scale that influences the timing and duration of REM sleep.

**Disclosure**: No

## O112/P991 | Sleep and traumatic brain injury

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Traumatic brain injury (TBI) is a major health concern associated with adverse outcomes and significant costs borne by patients, payers, and society. Of the adverse sequelae following TBI, sleep disorders like insomnia and obstructive sleep apnea affect 24%–75% of TBI patients – twice the prevalence among adults in the general population. Sleep disorders can cause, exacerbate, or prolong the most serious sequelae of TBI including post-traumatic stress disorder (PTSD), depression, chronic pain, poor cognitive performance, and diminished quality of life (See Figure 1). In part because early treatment of sleep disorders has been shown to prevent progression while improving mood and cognitive function after TBI, sleep disorders may be modifiable treatment targets to improve outcomes after TBI.

This overview will discuss sleep physiology, including the glymphatic system, a putative brain waste-clearance mechanism linked to sleep and shown in animals to be disrupted after TBI. It will also discuss novel biomarkers in development to measure this biology and accurately classify novel TBI-related sleep disorders. The talk will close with an exemplary clinical case and discussion of management strategies in accordance with the United States Defense Health Agency's TBI Center of Excellence (TBICoE) clinical recommendations, for which I was a coauthor.

**Methods/Results**: A review of TRACK-TBI prospective longitudinal sleep trajectories and biomarkers predicting these trajectories will be presented. Sleep-related epidemiologic and physiologic changes observed after TBI will be integrated with a presentation of novel approaches to examine sleep and the glymphatic system. Unpublished data using blood biomarkers and brain water measurements captured during sleep may be presented – depending on the scope preference of the committee.

**Conclusion**: Military operations and exposures such as TBI predispose warfighters to multiple sleep disorders, which may have unique pathophysiology that demands detailed investigation and characterization for preventative and treatment development. Measurement and enhancement of sleep physiology, such as the glymphatic system, which appears to have important links to sleep, stress, and TBI, may hold important implications for human performance and military readiness.

**Disclosure**: No

## O132/P992 | Hypnodensities: Predicting probability graphs of sleep stages

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The macro-structure of sleep dynamics is typically represented by a conventional hypnogram, which assigns a fixed label to every consecutive, non-overlapping 30 s windows of polysomnography (PSG) data. This convention is problematic for many reasons, one of which is the assumption that the underlying PSG content remains constant during the entirety of the epoch, which may not reflect true, underlying physiological activity. Current AASM guidelines on sleep stage scoring do not currently take this into account, resulting in epochs potentially including content from several sleep stages. This introduces uncertainties in the sleep stage scoring, which are not captured by the fixed-label hypnogram. In this roundtable session, we will present the hypnodensity as an alternative to conventional hypnograms. We posit that this will provide further insight into the dynamics of sleep by representing the hypnogram in a probabilistic sense. We will argue that a probabilistic representation of the hypnogram is desirable in characterizing sleep dynamics since the probabilistic representation of sleep epochs allow for mixed-state interpretations of sleep stages. We will show how this mixed-state representation can be used in downstream feature extraction schemes combined with probabilistic modeling for assisting in the diagnosis of narcolepsy type 1. Furthermore, by basing the hypnodensity prediction on an ensemble model, we can assess the uncertainty in sleep stage classification estimates by looking at the variance across the ensemble predictions. We will also discuss the important point of proper calibration of hypnodensities to ensure proper interpretation of sleep stage probabilities, as well as potential future research directions and applications.

**Disclosure**: No