an end-to-end fashion to avoid manual feature extraction. This allows for short prediction times and allows the model to learn more complex relations as the size of the training data increases. The model output is a temporal sequence of arousal probabilities, which are then used to generate discrete arousal events in a post-processing step. Furthermore, the output probabilities are calibrated to correct for the poor calibration of modern neural networks.
The model was trained and tested on over 1800 and 900 manually scored PSG and SAS sleep studies, respectively. The PSG data came from a population of patients referred to a sleep clinic by a medical doctor, but the SAS data from various research datasets.
Results: The ResTNet-Arousals model was validated on two previously unseen datasets. The first included traditional PSG sleep studies (N = 160, epochs = 119,774) and the other SAS sleep studies (N = 88, epochs = 70,349). On PSG data, the ResTNet-Arousal model achieved a positive percentage agreement (PPA) 68.82% (95%CI 63.87 - 69.67%) and a negative percentage agreement (NPA) 90.06% (95%CI 88.57 - 91.41%). The model had similar results when validated on data from SAS sleep studies, with a PPA of 68.10% (95%CI 65.52 - 70.64%), and an NPA of 94.48% (95%CI 93.33 - 95.46%).
Conclusions: The ResTNet-Arousal model shows good performance both for PSG and SAS sleep studies. Furthermore, a systematic comparison of manually scored arousals from different sleep clinics and the model predictions showed a systematic difference between the sleep clinics in the propensity to score arousal events; a manifestation of the low inter scorer agreement when scoring arousals.

SAMELISANT (SUVN-G3031), A HISTAMINE H3 RECEPTOR INVERSE AGONIST IN ANIMAL MODELS OF SLEEP DISORDERS

V. Benade [1], R. Abraham [1], R.C. Palacharla [1], S. Petlu [1], V.R. Mekala [1], S.K. Pandey [1], R.K. Badange [1], K. Bojja [1], V. Reballi [1], P.K. Achanta [1], P. Choudakari [1], R. Nirogi [1]. [1] *Suven Life Sciences Ltd, Hyderabad, India*

Introduction: Samelisant (SUVN-G3031) is a potent and selective H3 receptor (H3R) inverse agonist with hKi of 8.7 nM. It is selective against 70 other targets which includes GPCRs, ion channels, transporters, enzymes, peptides, steroids, second messengers, growth factors and prostaglandins. Samelisant exhibited desired pharmacokinetic properties and favorable brain penetration in preclinical species. Samelisant blocked R-α-methylhistamine induced dipsogenia in rats and increased *tele*-methylhistamine levels in brain and cerebrospinal fluid as well, which confirm its binding towards H3R.
Samelisant is currently being evaluated in a Phase-2 proof-of-concept study as monotherapy for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy with and without cataplexy (ClinicalTrials.gov Identifier: NCT04072380). In the current research work, samelisant was evaluated for neurotransmitter modulation and sleep wake profile in orexin knockout mice, a reliable animal model for narcolepsy.
Materials and Methods: In brain microdialysis, samelisant was evaluated for its effects on modulation of neurotransmitters like dopamine, histamine and norepinephrine in prefrontal cortex. In male orexin knockout mice, electroencephalography (EEG), electromyography and activity were monitored using telemetric device. Effects of Samelisant on sleep/ wake were evaluated during active period of animals. Animals were allowed recovery period of 3 weeks after surgery.
Results: Samelisant significantly increased histamine, dopamine and norepinephrine levels in the prefrontal cortex. Samelisant did not change dopamine levels in the striatal and accumbal brain regions. These results suggest that samelisant may not have propensity to induce abuse liability. Samelisant produced significant increase in wakefulness with concomitant decrease in non-rapid eye movement sleep in orexin knockout mice. It also significantly decreased number of cataplectic episodes in orexin knockout mice.
Conclusions: The results from non-clinical studies presented here provide a strong evidence for the potential utility of samelisant for the treatment of EDS and cataplexy in patients with narcolepsy.
Acknowledgements: None

SELECTIVE THERMAL STIMULATION TO MANIPULATE THE CIRCADIAN COMPONENT OF SLEEP REGULATION

S. Haghayegh [1,2,3], S. Khoshnevis [3], M.H. Smolensky [4,3], R.C. Hermida [5,3], R.J. Castriotta [6], E. Schernhammer [1,2,7,8], K.R. Diller [3]. [1] *Harvard Medical School, Boston, United States;* [2] *Brigham and Women's Hospital, Boston, United States;* [3] *The University of Texas at Austin, Austin, United States;* [4] *The University of Texas Health Science Center, Houston, United States;* [5] *University of Vigo, Vigo, Spain;* [6] *University of Southern California, Los Angeles, United States;* [7] *Harvard TH Chan School of Public Health, Boston, United States;* [8] *Medical University of Vienna, Vienna, Austria*

Introduction: Borbély's two-process model of sleep regulation entails circadian rhythm Process C and homeostatic sleep pressure Process S. We developed a novel thermal sleep system composed of selective thermal stimulation (STS), i.e., mild heating (39°C) of the skin over the cervical spine to manipulate blood flow to the dense network of arteriovenous anastomoses (AVAs) of the glabrous skin, e.g., hands and feet, plus a dual-temperature zone mattress with a warmer (33°C) peripheral zone to improve vasodilation of AVAs on the hands and feet and a cooler central (27°C) zone to enhance heat transfer by conduction from the central body core to the environment. We hypothesized this novel thermal sleep system, which increases heat transfer by redistributing blood flow from the body core to the glabrous skin, increases the distal-proximal-gradient temperature (DPG) and reduces core body temperature (CBT), elements of Process C, resulting in shortened sleep onset latency (SOL) and improved sleep quality.
Materials and Methods: After acclimating to the study environment and conditions through an afternoon nap, 11 healthy normal sleeper males, 23.6±3.9 [mean±SD] years of age, were randomly subjected to two non-consecutive nocturnal sleep sessions -a treatment night with the thermal sleep system activated and a control night with it deactivated. Participants were challenged to go to bed (lights-out) two hours earlier than usual. Data collection commenced 45 min before lights-out to establish baseline values of the study variables. On the treatment night, the dual-temperature zone mattress was activated during the entire sleep period, while the STS pillow was activated only during the first 30 min.
Results: There was no significant difference between the control and treatment nights in the baseline values of glabrous skin blood flow (GSBF), DPG, and CBT. During the first 30 min after lights-out on the treatment night, when both the STS pillow and dual-temperature zone mattress were activated, GSBF (Δ=49.77±19.13 PU, P=0.013, Cohen's d=0.85) and DPG (Δ=2.05±0.62°C, P=0.005, Cohen's d=1.10) were significantly higher and CBT (Δ=-0.15±0.07°C, P=0.029, Cohen's d=0.58) was significantly reduced compared to the control night. Moreover, the SOL was significantly shorter (Δ=-48.6±23.4 min, P=0.032, Cohen's d=0.83), and participants rated their subjective sleep quality statistically significantly better (P<0.001) on the treatment night than on the control night.
Conclusions: This proof-of-concept study supports the proposed hypotheses that the dual-temperature zone mattress, which maintains high blood flow in the glabrous skin (via the warm peripheral zone) and increases conductive heat transfer from the body core to the environment (via the cooler central zone), in combination with STS resulting in increased GSBF and DPG and decreased CBT, with beneficial effects being shortening of the SOL through re-enforcement of Process C plus improvement of sleep quality that is consistent with diminution of the sleep pressure of Process S.
Acknowledgements: This research was sponsored in part by the Robert and Prudie Leibrock Professorship in Engineering at UT Austin. UT Austin owns patent rights to intellectual property relating to the technologies described in this article.

SLEEP AND SHOUTS: THE INTRINSICALLY AVERSIVE NATURE OF ROUGH SOUNDS IS PRESERVED DURING NREM SLEEP

G. Legendre [1], M. Moyne [2], J. Dominguez-Borras [3], V. Sterpenich [1], D. Grandjean [4,5], S. Schwartz [1,4], L. Arnal [6]. [1] *University of Geneva, Department of Basic Neuroscience, Geneva, Switzerland;* [2] *EPFL, Geneva, Switzerland;* [3] *University of Barcelona, Department of Clinical Psychology and Psychobiology, Barcelona, Spain;* [4] *University of Geneva, Swiss Center*

for Affective Sciences, Geneva, Switzerland; [5] *University of Geneva, Department of Psychology, Geneva, Switzerland;* [6] *Institut Pasteur, Departement of hearing, Paris, France*

Introduction: Screams are powerful vocalizations that are intrinsically aversive in humans. These vocalizations are characterized by a high roughness, an acoustic dimension which is potentially at the root of the aversiveness of screams. Current knowledge posits that this simple acoustic feature serves to alert conspecifics about the presence of a danger. It induces the urge to act, while generating strong and negative emotions. Here, we hypothesized that roughness should still be processed as an alarm signal in states of reduced responsiveness. We investigated this question by playing recorded screams to sleeping participants.
Materials and Methods: We acquired electroencephalography (EEG) data in 12 participants during wakefulness and during a full night of sleep while we played screams (with various levels of roughness) at a low intensity to the participants. We also presented pitch- and intensity-matched control vocalizations without roughness. We then compared the evoked brain responses to the two types of vocalizations by analyzing the event-related potentials and time-frequency decomposed responses.
Results: At wakefulness and during NREM sleep, we found that screams at a low intensity generated brain responses that are better time-locked, hence more consistent in time, than control vocalizations. In addition, screams evoked more sleep spindles. Finally, a regression with the roughness and pitch of vocalizations revealed that spindle generation was linked to sound roughness but not pitch.
Conclusions: Our results suggest that the response to screams is more reliable than to controlled vocalization across both wakefulness and sleep, thus consistent with screams representing powerful and pervasive alarm signals in humans. In addition, the link between acoustic roughness and spindle generation supports a link between stimulus emotional relevance and spindle generation during sleep, a relation that is receiving increasing attention in the litterature. This study shows that, beyond loudness, acoustic roughness, which is produced by numerous human activities (e.g., snoring, traffic noise, construction work), should be measured and strongly avoided in the proximity of sleeping environments.
Acknowledgements: This work was supported by the National Center of Competence in Research (NCCR) Affective Sciences (financed by the Swiss National Science Foundation, 51NF40-104897; and hosted by the University of Geneva), the Private Foundation of the University Hospital of Geneva (grant number: CONFIRM RC1-23) and by grants from the Swiss National Science Foundation (320030-159862 to S.S.; Ambizione - PZ00P3-148112 to J.D.B.).

SLEEP AND THE MENSTRUAL CYCLE: A REVIEW OF 48,720 CYCLES

N. Thigpen [1], N. Gotlieb [2], K. de Mesa [3], C. Kryder [4], S. Patel [2]. [1] *Oura, Algorithm Development, San Francisco, United States;* [2] *Oura, Science, San Francisco, United States;* [3] *Oura, Engineering, San Francisco, United States;* [4] *Oura, Science Communications, San Francisco, United States*

Introduction: The Oura Ring is a wearable health platform that enables users to track their sleep, heart rate, activity, menstrual cycles, and more. Here, we assess changes across the reproductive lifespan through sleep physiology and sleep behaviors in an Oura dataset containing 1.3 million nights of sleep summary data. This dataset contains 48,720 complete menstrual cycles from 7877 unique Oura ring users.
Materials and Methods: Metrics explored include daily summaries of physiology while asleep, i.e., body temperature, respiratory rate, heart rate, and heart-rate variability (HRV), and also sleep behaviors, i.e., sleep duration, midpoint, and the number of awakenings. Metrics were compared statistically via a mixed ANOVA with a two-level within-participant factor of menstrual cycle phase (luteal or follicular) and six-level between-participant factor containing age groups between 18 and 47. To demarcate the menstrual cycle phases, period onset and ovulation were either labeled by the user in the Oura app or automatically detected via the user's continuously measured body temperature.
Results: As expected, body temperature robustly increased in the luteal phase relative to the follicular phase as shown by a large main effect ($\eta p2 >$ .9). Respiratory rate and heart rate were also reliably higher during the luteal phase (both with large effect sizes, i.e. $\eta p2 >$ .7). Neither respiratory rate nor heart rate showed main effects of age, but heart rate did show a moderate interaction with age across the menstrual cycle, suggesting that as users age their heart rate during sleep is more stable across the menstrual cycle phases. HRV consistently decreased in the luteal phase relative to the follicular phase as shown by a large main effect of menstrual cycle phase ($\eta p2 >$ .4). HRV also showed monotonic decreases with age from an average of 60 ms at age 18 to 40 ms by age 47. HRV had a small but significant interaction between age and menstrual cycle phase, such that HRV in younger users had a stronger association with the phase of their menstrual cycle. Users approaching menopausal ages also exhibited more perturbed sleep, as seen in shorter sleep durations ($\mu = 12$ minutes), earlier bedtimes ($\mu = 41$ minutes), and increased awakenings ($\mu = 5\%$).
Conclusions: Overall, the Oura Ring reliably captures changes in physiology during sleep across the menstrual cycle and demonstrates how these patterns change across the reproductive lifespan. The interactions of HR and HRV between the menstrual cycle and age are consistent with what would be expected with decreasing progesterone levels as users approach menopause. These findings suggest that HR and HRV may be particularly suitable candidates to help detect early signs of menopause or fertility issues. To our knowledge, this is the largest dataset of its kind and thus these results can guide sleep-based algorithms in accounting for the menstrual cycle and aging across the reproductive lifespan. For future applications, this work provides the foundation to detect abnormal menstrual cycles, monitor sleep interventions outcomes in menopausal women, build custom workouts for female athletes, detect early signs of declining fertility, and more.

SLEEP EEG SPECTRAL EXPONENTS AND MAXIMAL PEAK FREQUENCIES IN CONSECUTIVE NREM PERIODS: POSSIBLE MARKERS FOR SLEEP REGULATION

C.G. Horváth [1], O. Szalárdy [1], P.P. Ujma [1], P. Simor [2], F. Gombos [3], I. Kovács [3], M. Dresler [4], R. Bódizs [1]. [1] *Semmelweis University, Institute of Behavioural Sciences, Budapest, Hungary;* [2] *Eötvös Loránd University, Budapest, Hungary;* [3] *Pázmány Péter Catholic University, Budapest, Hungary;* [4] *Radboud University, Nijmegen, Netherlands*

Introduction: According to Borbély (1982) a homeostatic and a circadian process define the main aspects of sleep regulation. Although slow wave activity of the sleep EEG is a widely accepted marker of sleep homeostasis, high frequency activity is also changing throughout the night (in the opposite direction). Thus, the ratio of lower to higher frequencies in the EEG power spectrum seems to be a more accurate indicator of sleep homeostasis. In addition, sleep spindle frequency could be a suitable marker of the circadian process since it was shown to follow a U-shaped overnight dynamic and its dampening in aged subjects.
Given the linear association between the logarithm of frequency and logarithm of amplitude the Fourier spectrum can be described by an approximation of the parameters of the following function: $P(f) = Cf^{\alpha} P_{Peak}(f)$, where P is power as a function of frequency, C is the constant, α is the spectral exponent which shows the ratio of different frequencies in the signal, and P_{Peak} is the peak power at frequency f. We hypothesized that (i) $P_{peak}(f)$ values of the sleep spindle range (9-18 Hz) are higher in the last and first sleep cycles than in the middle parts of night sleep records, (ii) spindle deceleration in the middle of the night is modulated by age, while (iii) α is decreasing linearly across the night as the sleep pressure decays (spectral slope flattening).
Materials and Methods: Artefact-free NREM sleep periods of successive cycles in the Budapest-Munich database of sleep records ($N = 251$ healthy subjects, 122 females, age range: 4–69 years) were analysed by FFT routine and power spectrum obtained for selected EEG derivations. Furthermore, the log-log power was fitted with a linear, and a peak detection was applied in the 9-18 Hz (broad sleep spindle) range at derivations O2, O1, P4, P3, C4, C3, F4, F3, Fp2, Fp1. Statistical analysis was based on general linear models.
Results: The NREM sleep EEG spectral exponents (α) increased in consecutive sleep cycles (absolute values decreased), and this effect was significant at all derivations. The maximum peak frequency was significantly modulated by age at all derivations and by cycle at O2, P4, P3, C4, F4, F3, Fp1. There was a cycle x age group interaction at derivations O2 and F3.