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SOURCES OF VARIATION IN THE SPECTRAL SLOPE OF THE SLEEP EEG

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Introduction: The 1/f spectral slope of the electroencephalogram (EEG) estimated in the gamma frequency range has been shown to reflect neural excitation/inhibition ratio and synchronization level within local neural populations. It was proposed as an arousal marker that differentiates wake, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. These stages exhibit progressively steeper 30-45 Hz slopes, interpreted in terms of increasing cortical inhibition. Here we sought to replicate these findings in a larger sample and provide a comprehensive characterization of how slope changes with age, sex, and its test-retest reliability as well as potential confounds that could affect the slope estimation.

Methods: After stringent exclusions and quality control, our final sample included 10,255 whole-night polysomnograms (PSGs) on 7,312 individuals 2,943 of whom had a second PSG, from the National Sleep Research Resource (NSRR). All preprocessing steps were performed using an open-source Luna package and the spectral slope was estimated by fitting log-log linear regression models on the absolute power from 30 to 45 Hz separately for wake, NREM and REM stages. We described sources of variation in the spectral slope (both within and between individuals) and its relationship to other sleep parameters including power and interhemispheric coherence.

Results: There was unambiguous statistical support for the hypothesis that, within individuals, the mean spectral slope grows steeper going from wake to NREM to REM sleep. We found that the choice of mastoid referencing scheme modulated the extent to which electromyogenic or electrocardiographic artifacts were likely to bias 30-45 Hz slope estimates, as well as other sources of technical, device-specific bias. Nonetheless, within individuals, slope estimates were relatively stable over time. Both cross-sectionally and longitudinal, slopes tended to become shallower with increasing age, particularly for REM sleep; males tended to show flatter slopes than females across all states. Although conceptually distinct, spectral slope did not predict sleep state substantially better than other summaries of the high-frequency EEG power spectrum (>20 Hz, in this context) including beta band power, however. In contrast to the common conception of the REM EEG as relatively wake-like (i.e. 'paradoxical' sleep), REM and wake were the most divergent states for multiple metrics, with NREM exhibiting intermediate profiles. Under a simplified modeling framework, changes in spectral slope could not, by themselves, fully account for the observed differences between states, if assuming a strict power-law model.

Conclusion: Although the spectral slope is appealing, theoretically inspired parameterization of the sleep EEG, we underscore some practical considerations that should be borne in mind when applying it in diverse datasets. Future work will be needed to fully characterize state-dependent changes in the aperiodic portions of the EEG power spectra, which appear to be consistent with, albeit not fully explained by, changes in the spectral slope.

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INTEGRATED ACTIGRAPHY-BASED BIOMARKER FOR THE RISK OF ALZHEIMER'S DEMENTIA

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Introduction: Many physiological measures derived from actigraphy including physical activity, sleep, circadian/daily rhythm, and temporal correlations have been shown to predict Alzheimer's dementia (AD). This study aimed to combine these actigraphy-based measures to develop an integrated actigraphy biomarker (IAB) for AD and to test its link to the genetic risk for AD.

Methods: We analyzed data of 1107 participants (age 80.9±7.3(mean±SD)) from the Rush Memory and Aging Project who were non-demented and had actigraphy (~10 days) at baseline, and had annual cognitive assessment during the follow-up (1-15 years). 270 developed AD (mean = 7.4 years). To construct the IAB for the AD's risk, we trained a random forest survival model, in which time to incident AD was the outcome, and inputs included 10 features derived from actigraphy data: physical activity level, 3 features for sleep (sleep duration, sleep fragmentation, activity fragmentation), 4 features for circadian rhythmicity (amplitude, acrophase, interdaily stability, and intradaily variability of 24-hr rhythms), and 2 features for temporal correlations (at timescales between 1-90 min and 120-480 min). Polygenic risk score (PRS) was calculated using 457 independent SNPs strongly associated with Alzheimer's disease ($p<0.001$). Cox proportional hazard ratio models were performed with different combinations of IAB, PRS, age, sex, and education, and the concordance score (C-score) was used to evaluate model performance.

Results: The derived IAB was 0.6 SD larger in the AD group as compared with the controls. The IAB alone achieved a C-score = 0.61 in predicting AD, with a hazard ratio=1.5 for 1-SD increase in IAB. The IAB and PRS were not correlated ($r2=0.0004$, $p=0.25$), and both significantly contributed to the prediction (both $p<=0.0001$) when included in one model, giving a C-score of 0.65. C-score was 0.7 in the model using only age, sex and educations yielded, and increased to 0.74 after including IAB and PRS (both effects remained significant $p<0.0001$).

Conclusion: The integrated actigraphy biomarker may provide complementary information for early prediction and detection of AD, independent of the known demographic and genetic risk factors.

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RETINAL RESPONSIVITY IS ASSOCIATED WITH CIRCADIAN PHASE AND CIRCADIAN ALIGNMENT BUT NOT SLEEP TIMING

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Introduction: Light entrains the central circadian clock, with projections from the retina to the SCN through melanopsin-containing retinal ganglion cells (ipRGCs). Altered responsivity to light

reflects ipRGC functioning and may be a physiological vulnerability for disrupted photoentrainment. Understanding how retinal responsivity relates to sleep and circadian timing may inform who might most benefit from sleep and circadian interventions.
Methods: 64 participants (85 observations) ages 20-66 years old were recruited during winter (n=35) and summer months (n=50), and included individuals with seasonal depression (n=33) and nonseasonal, never depressed controls (n=31). The post-illumination pupil response (PIPR) to red and blue light was used to measure the responsivity of ipRGCs (average 1:30pm; 10am-7pm). Circadian phase was assessed using Dim Light Melatonin Onset (DLMO), collected every 30-minutes on Friday evenings. Midsleep timing was measured using actigraphy (average number nights=4), and circadian alignment was calculated as the DLMO-midsleep phase angle. We performed a multilevel regression to determine the relationship between PIPR and markers of sleep and circadian timing, accounting for repeated seasonal assessments with a random intercept of participant. Covariates included age, gender, diagnostic group, and circadian time of PIPR assessments. We ran sensitivity analyses including photoperiod length on the day of PIPR assessment to account for potential light exposure on the PIPR.
Results: Greater retinal responsivity was associated with later DLMO (b=4.45; partially standardized b=0.28; SE=1.84; p=0.03), and shorter DLMO-midsleep phase angle (b= -7.33; partially standardized b= -0.32; SE=2.51; p=0.004), but not midsleep (b= -3.44; partially standardized b= -0.14; SE=2.35; p>0.05). Individuals with later DLMO had PIPR assessments at earlier circadian times (b= -0.12; SE=0.04; p=0.01). Older participants (b= -0.04; SE=0.02; p=0.04) and controls (b= -0.95; SE=0.44; p=0.04) had earlier sleep midpoints, but covariates were not associated with circadian markers. The association between circadian timing and PIPR became nonsignificant (b=4.15; partially standardized b=0.26; SE=1.88; p=0.06) when including photoperiod.
Conclusion: Retinal responsivity was associated with circadian but not behavioral sleep timing, suggesting ipRGC functioning may have downstream effects on circadian entrainment. Assessing circadian variation of retinal responsivity remains a crucial next step prior to testing whether retinal responsivity impacts response to circadian-focused interventions.
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INCREASED BRAIN KYNURENIC ACID ELICITS SEX-DEPENDENT ABNORMALITIES IN NREM SLEEP SPINDLE DYNAMICS

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Introduction: Sleep spindles are thalamocortical oscillations which occur during non-rapid eye movement (NREM) sleep. NREM sleep spindle aberrations are a consistent clinical sleep deficiency associated with psychotic disorders and exacerbation of cognitive symptoms. Kynurenic acid (KYNA), a tryptophan metabolite synthesized from kynurenine via kynurenine aminotransferases (KATs) and modulator of glutamatergic and cholinergic neurotransmission, is elevated in the brain of patients with psychotic disorders, including schizophrenia and bipolar disorder. Currently, we sought to understand the neurodevelopmental and transient impacts of brain KYNA elevation on sleep spindle dynamics.
Methods: In Experiment #1, sleep spindles were evaluated in adult offspring, postnatal day (PD) 56 from embryonic kynurenine (EKyn) treated rat dams (Rentschler et al., 2021 Sz Bull) (N=7-9 per group). EKyn KYNA male, but not female, offspring have elevated KYNA during the light phase (Wright et al., 2021 Frontiers in Psychiatry). In Experiment #2, sleep spindles were evaluated in adult rats injected with kynurenine (100 mg/kg; i.p.) to acutely elevate brain KYNA levels at zeitgeber time 0 (N=8-12 per group). Polysomnography was recorded via EEG/EMG telemetry. Sleep spindles were evaluated using a custom-made manual scoring system during the first 4 hr of the light cycle.
Results: Male EKyn, but not female, exhibited a decrease in spindle density compared to ECon (2-wayANOVA: ***P<0.001). FFT spectral power for peak spindle frequency (10-15 Hz) was reduced for all EKyn offspring (3-way ANOVA; frequency x treatment interaction: ****P<0.0001; treatment: *P<0.05). Kynurenine challenge reduced spindle density for both sexes (2-way ANOVA: ***P<0.001; M: **P<0.01; F: *P<0.05). Frequency x treatment interaction for males (2-way ANOVA: ***P<0.001) was observed with lower FFT spectral power for 10-10.5 Hz (*P<0.05) and greater power for 14-14.5 Hz (*P<0.05).
Conclusion: We determined conspicuous sex differences in spindle dynamics in the EKyn paradigm that may be related to brain KYNA levels; only males exhibited a decrease in spindle density, however all EKyn offspring had reduced FFT spectral power. Kynurenine challenge reduced spindle density in both sexes, however only males had changes in FFT spectral power. Future work will consider the efficacy of KYNA synthesis inhibition to prevent NREM sleep spindle abnormalities induced by KYNA elevation.
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REMOTE SALIVA SAMPLE COLLECTION FOR DIM LIGHT MELATONIN ONSET (DLMO) MEASUREMENT IN URBAN CHILDREN WITH ASTHMA DURING THE COVID-19 PANDEMIC

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Introduction: The COVID-19 pandemic has challenged researchers to use remote data collection. Our project includes determining DLMO phase, requiring a family-friendly without face-to-face interaction. We describe here our protocol, experiences, lessons learned, and findings from the first 15 participants.
Methods: Fifteen urban-dwelling children with moderate to severe persistent asthma [7 girls, ages 7 (n=1) to 10 years; and 8 boys, 8 or 9 years] and caregiver (CG) participated. CG tracked bedtimes and risetimes in daily diaries for 10-14 days; average bedtimes from 5 nights preceding saliva collection were used to determine timing for 10 half-hourly samples. CG and child were oriented and then watched a demo video. A "spit-kit" was delivered to the home the afternoon of the study. Kits included a small cooler bag with bottle of water, 10 numbered and 5 spare Salivette tubes (Starstedt, Germany), plastic bag, dark wraparound glasses with securing strap, and log sheet. Data collection began with a zoom call with staff, CG, and child to reiterate the instructions, answer questions, and observe the first sample. Thereafter, a staff member telephoned the caregiver every 30 minutes to prompt the next sample and query whether glasses had been kept on. CG placed kit outside the home for morning pick up. Samples were centrifuged and frozen (-20°) until sending to the assay lab (SolidPhase, Portland, ME) for melatonin radioimmunoassay (Alpco, Windham, NH).