Power-law parametrization of the sleep electroencephalography spectra: a new framework for modelling sleep-wake regulation

Ph.D. thesis

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1. Introduction

The most widely used conceptual framework for understanding sleep-wake regulation is the two-process model proposed by Alexander Borbély, assuming a role of a homeostatic, sleep-history-dependent mechanism and a circadian rhythm. The homeostatic process represents sleep pressure, which is hypothesized to build up during wakefulness and to deplete during sleep, fluctuating within a range that is typically in alignment with the day-night cycle reflected by the circadian pacemaker. As originally proposed, the circadian oscillator is independent of sleep-wake history and mostly plays a role in the timing of the sleep episode. In this model the sleep homeostat was entirely based on slow wave activity (SWA, the electroencephalography (EEG) activity in the 0.75–4.5 Hz frequency range) as it appears to best reflect the classical concept of homeostasis by maintaining the balance within the sleep-wake cycle. Circadian process, however, was only postulated in form of a sine function, fitted to the 24-hours day.

The examination of the two processes by polysomnography (PSG) remains unresolved. Firstly, no validated EEG marker exists for the circadian process, although spindle frequency has been shown to reflect circadian variation in several studies. Furthermore, there are two major criticisms regarding SWA as a homeostasis marker. SWA cannot be standardized, preventing the establishment of normative values for optimal sleep. In addition, other frequency bands also change as a function

of sleep pressure; thus, SWA in itself is necessary but may not be sufficient for modelling homeostasis.

Neurophysiological signals consist of rhythmic oscillatory activities and an aperiodic component. The scalp EEG power spectrum follows a power-law distribution which implies a linear relationship between the logarithms of amplitude and frequency of the periodogram. This 1/f pattern represents the aperiodic aspect of the signal, stemming from the inherent scale-free nature of power-law functions. Essentially, this suggests that the slope of the spectrum reveals the overall frequency distribution within the time series, providing the constant ratio between lower and higher frequency power. Periodic activity occurs in particular frequency ranges of the power spectrum, making it essential to properly separate these two components for a precise characterization of sleep EEG.

We hypothesize that the spectral slope is a reliable marker of the homeostatic process of sleep regulation. It is likely more standardisable than the gold-standard (as reported values vary within a much narrower range compared to SWA) while still capturing interindividual differences (such as age), and accounts for the entire frequency composition of the spectrum.

On the other hand, obtaining the spectral peak frequency in the spindle band (broad sigma range: 9–16 Hz) using spectral parametrization procedures, would greatly simplify the investigation of the circadian process of sleep regulation.

2. Objectives

The overall objective of my PhD research was to characterize the non-rapid eye movement (NREM) sleep

EEG Fourier spectrum by considering its power-law scaling properties, with a primary focus on how the derived parameters can be captured within the context of sleep regulatory processes. To achieve these objectives, the presented studies set out to accomplish the following:

In the first study, we aimed to demonstrate that the parametrization procedure effectively reduces the typically analysed 191 spectral measures to just 4 (spectral slope, intercept, amplitude and frequency of the largest peak in the spindle frequency range), which reliably capture the known age-, sex-, and intelligence-related associations of the sleep EEG.

The second study examined the overnight dynamics of those 4 parameters, focusing on the first four consecutive sleep cycles of habitual PSG recordings. The aim was to investigate whether separating the aperiodic and periodic components of the NREM spectra could reveal reliable indicators of known overnight sleep cycle dynamics associated with sleep regulatory processes. The main research question was whether spectral slope is more standardizable than the gold-standard SWA, as well as whether spindle peak frequency evolves in a U-shaped curve during the night, a pattern suggesting a circadian modulation of that metric.

Finally, Study 3 aimed to validate the role of spectral parametrization in examining sleep regulatory processes using a 35-hour home sleep deprivation protocol with chronotype-dependent baseline sleep (BS) onsets. The main objective was to assess spectral slope and peak frequency by challenging the homeostatic process (sleep deprivation) and slightly advancing sleep onset, with the

aim of unravelling the circadian rhythm (reschedule of recovery sleep (RS) by advancing it with ~ 4.5 hours).

3. Methods

3.1. Study 1 and 2

Both study 1 and 2 were retrospective studies with an overlapping sample derived from a database constitutes of N = 251 healthy individuals (122 females, age range: 4-69 years). However, in study 1, data from children under the age of 17 were excluded, resulting in N=175 participants (81 females).

Polysomnography was measured in two consecutive nights, with EEG electrode locations according to the international 10-20 system and a mathematically-linked mastoid reference. All PSG data were marked for artefacts and scored based on the standard criteria of sleep wake states manually. Power spectral density was calculated by mixed-radix fast Fourier transform following a Hann-window for every 4-seconds of non-artefactual EEG with 50% overlap. Subsequently, EEG-location specific power spectral densities from all 4-second windows were averaged for NREM phases of the entire night (Study 1) or within the successive sleep cycles (Study 2).

A spectrum parametrization procedure was applied to separate aperiodic and periodic parts of the EEG spectra resulting in four metrics: spectral slope, intercept and peak properties (frequency and amplitude). Main steps of the method are the following:

1. Piecewise cubic Hermite interpolation of the log–log scale of NREM (N2 and N3) sleep EEG spectra to equidistant, 0.0052 Hz bins

2. Estimation of spectral slope by fitting a linear function to the spectrum, excluding frequency bins below 2 Hz and between 6–18 Hz, to prevent fitting bias caused by non-random oscillatory activity in those frequency ranges.
3. Detection of spectral peaks in the 9–18 Hz frequency range, known as broad sigma range. Peak detection was defined as searching for local maxima and minima in mathematical terms within the sigma range.

Anterior-posterior changes in peak frequency were tested by the calculation of the differences in peak frequencies of all adjacent antero-posterior regions. Thus, positive values indicate anterior-posterior increases. Successive frequency changes were summed per subject, which was then averaged across the sample. The maxima were also identified and localized individually, yielding a sample mean of maximal shift and its topographical distribution.

3.2. Study 3

N=46 healthy young adult participated in a 35-hour long sleep deprivation study. Inclusion criteria were based on self-reports and included healthy sleep, a non-extreme circadian rhythm patterns (measured by Munich Chronotype Questionnaire (MCTQ)), and lack of psychiatric, and neurological disease, as well as acute or chronic illnesses. Final analyzable sample comprised N=38 participants (age range:18–39 years, 19 females).

EEG-recorded sleep was performed at the home of the participants with Hypnodyne corp. Zmax mobile EEG headband which records EEG signal at F7-Fpz and F8-Fpz with sampling rate of 256 Hz. These were re-referenced to

their common average. During the BS measurement, participants were free to choose their bedtime, allowing them to follow their own sleep preferences. After BS, the 35-hour sleep deprivation began. Participants were required to maintain continuous contact with the experimenter. Additionally, experimenters visited participants in their homes at the 24^{th} and 34^{th} hour of the sleep deprivation period in person.

PSD was estimated based on the Welch method, using Hann window for 4-second segments with an overlap of 50%, and Fast Fourier Transform for NREM sleep (stages: N2 and N3) in each sleep cycle separately. SWA was determined by summing the PSD values within the 0.75–4.5 Hz range of EEG activity from the averaged N2 and N3 episodes across complete sleep cycles.

Spectral parametrization was conducted by the fitting oscillations and one over f (FOOOF) method in Study 3 within the same fitting range as in study 1 and 2 (2–48 Hz).

3.3. Statistical analyses

All statistical analyses were carried out with TIBCO Statistica 13 software. Parametric tests were performed for normally distributed data, while non-parametric tests were applied for non-Gaussian distributions. Normality was assessed using the Shapiro-Wilk test in all cases.

In study 3, besides building GLMs to analyse the first 4 sleep cycles of the entire sample, we also created subgroups based on the number of sleep cycles participants had, separately in BS and RS. This approach made it possible to analyse the overnight dynamics across the entire night for each participant with full recordings.

Since the cycle effect was expected to be substantial, we deemed a group analysable if it had a minimum sample size of N = 7.

4. Results

4.1 Study 1 and Study 2

4.1.1. Main characteristics of the power-law parametrized metrics during habitual sleep

Spectral slope sample mean of the whole sleep records (N2 + N3 stages) of 175 healthy participants, measured across up to 18 common EEG derivations, ranged from -2.73 (SD=0.22, at recording location: Fz) to -2.33 (SD=0.22, at recording location T5), whereas the mean of intercepts (lnC) varied between 5.67 (SD=0.69, T5) and 3.74 (SD=0.73, Fz). As these aperiodic components are strongly and negatively correlated, that is steeper spectral slopes reflected higher intercepts (Pearson's r ranged between -0.85–(-0.76), $p<0.001$ across electrode locations), the present thesis mainly focuses on the spectral slope and the spindle peak characteristics (amplitude and frequency) (except for the case characterized by a non-shared statistical effect involving the intercept).

The presence of at least one peak was observed in 81.16% to 100% of participants, varying by EEG recording site. The largest peak (with the highest whitened amplitude) in this frequency range aligned with the general topographical-frequency distribution characteristic of sleep spindles. Specifically, spectral peaks in anterior regions appeared at lower frequencies

compared to those in posterior areas. The total increase in the frequency of the largest peak along the antero-posterior cortical axis was 1.99 Hz in average across subjects. However, this frequency shift was not gradual; instead, more than 83% (1.67 Hz) of the total increase occurred as a discrete jump indicating the presence of fast and slow sleep spindles at different EEG locations.

Overnight dynamics of the four metrics were tested by dividing sleep into sleep cycles and the first 4 cycles were analysed (average number of cycles was m=4.25). GLM revealed a U-shape-like overnight dynamic of peak frequency ($F=11.65$, $p<0.001$). Furthermore, electrode location impacted this effect (cycle × region: $F(12,2172)=5.34$, $p<0.001$), indicating lower peak frequencies in the frontopolar regions during the second and third sleep cycles compared to the first and fourth (Figure 1).

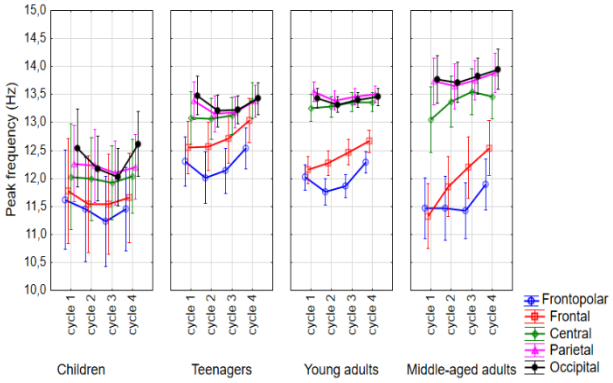

Figure 1. Cycle dynamics of the frequencies of the largest peaks in the spindle range.

On the other hand, significant main effects indicated that earlier cycles and more anterior brain region imply steeper spectral slopes (F=210.78, p<0.001; Figure 2) and lower peak amplitudes (F=78.45, p<0.001).

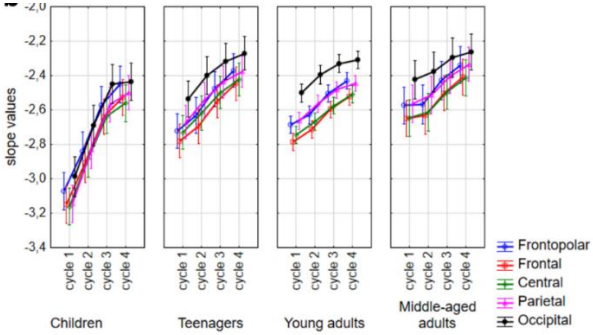

Figure 2. Spectral slope as a function of sleep cycles, age and recording sites.

4.1.2. Age

The analysis of the whole sleep records revealed that age positively associates with spectral slope at all, and negatively with peak amplitudes and peak frequencies at F3, F4, Fz, C3, C4, Cz, P3, P4, T5, T6 and Fp1, Fp2, F3, F4, Fz, F7, F8, T4 EEG locations. In the analyses where sleep was divided to cycles, we also found significant main effect of age on spectral metrics, revealing that younger age predicts steeper spectral slope (F=17.05, p<0.001), lower maximal peak amplitudes (F=11.93, p<0.001) and slower spindle frequency (F=10.34, p<0.001).

4.1.3. Sex

Women had higher intercepts and peak frequencies (p<0.05, except for T3 and T4 locations; Figure 3) than man, and the two sex groups did not differ in terms of the

whitened spindle peak amplitude or slope at any derivations (p>0.05).

4.1.4. IQ

Pearson correlation was significant in women between peak amplitudes and IQ (Figure 1), at the following recording sites: C3 (N=67, r=0.33, p=0.007), C4 (N=66, r=0.34, p=0.005), Cz (N=55, r=0.34, p=0.010), P3 (N=68, r=0.26, p=0.031), P4 (N=68, r=0.28, p=0.020), and T3 (N=45, r=0.32, p=0.031). No significant associations were found in men (Figure 3).

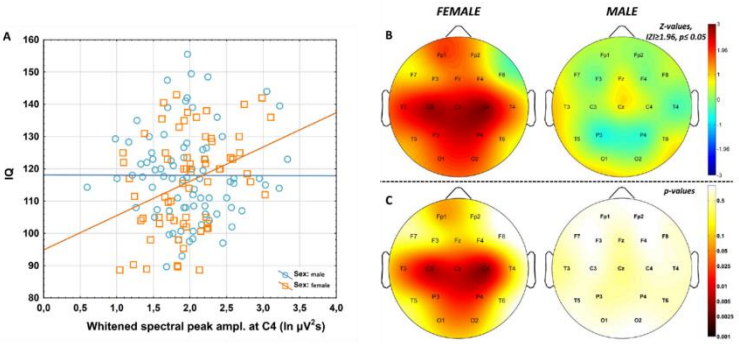

Figure 3. Correlations between NREM sleep EEG spindle frequency whitened spectral peak amplitudes and IQ in females and males.

4.1.5. Relationship between the spectral slope and the gold-standard homeostatic marker, SWA

Pearson correlation (focusing on the F3 electrode) revealed a significant negative, moderate-to-strong associations between the natural logarithm of SWA (lnSWA) and the spectral slope in all sleep cycles (Cycle 1: $N = 251$ $r = -0.73$, $p < 0.001$; Cycle 2: $N = 251$ $r = -0.61$, $p < 0.001$; Cycle 3: $N = 249$ $r = -0.56$, $p < 0.001$; Cycle 4: $N = 240$ $r = -0.56$, $p < 0.001$). To test the

interindividual differences in both metrics, the coefficients of variation were estimated. Results revealed an approximately 2-to-3 times as high coefficients of variation for lnSWA as compared to the spectral slopes in all four cycles (Table 1) suggesting larger interindividual variability in the gold-standard metric.

Table 1. Coefficients of Variation of EEG lnSWA and spectral slopes.

	cycle	Valid N	Mean	Std.Dev.	**Coef.Var.**
ln SWA + 4	1	251	10.65	0.81	**7.64**
	2	251	9.68	0.81	**8.38**
	3	249	8.85	0.84	**9.46**
	4	240	8.18	0.91	**11.11**
slope + 4	1	251	6.82	0.25	**3.72**
	2	251	6.72	0.23	**3.38**
	3	249	6.58	0.21	**3.16**
	4	240	6.50	0.21	**3.30**

4.2. Study 3

Due to technical issues, three BS and seven RS recordings were incomplete. These data were excluded from analyses involving the total length of the nights. The mean sleep duration was m_{BS}=7.9 (min-max: 5.8–10.7) hours in BS and m_{RS}=12.2 (min-max: 9.7–14.74) hours in RS, while the sample median of the number of sleep cycles increased from Mdn_{BS}=5 (min-max: 3–7) to Mdn_{RS}=8 (min-max: 6–10).

4.2.1. Effect of sleep deprivation on spectral slope

Spectral slope flattens during the first 4 cycles of sleep ($F=65.94$, $p<0.0001$) and it is significantly steeper in RS compared to BS ($F=98.25$, $p<0.0001$; Figure 4). Cycle

effect remained significant even when the whole-night sleep including all cycles was considered (Figure 7).

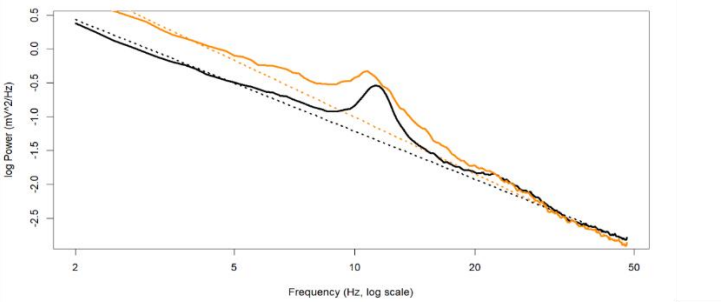

Figure 4. Spectrum of the first cycle of sleep for BS (black) and RS (orange), as well as the fitted aperiodic components with dashed lines in a 24-year-old male participant.

Furthermore, in line with the dynamic of the homeostatic process, RS C1 spectral slope was significantly steeper than BS C1 (BS: m=2.4, SD=0.1; RS: m=2.63, SD=0.2, $t(35)=-6.6$, $p<0.0001$), while no significant difference was detected between the slope values of the last sleep cycles in the two conditions (Figure 5).

4.2.2. Effect of sleep deprivation on SWA

Similar to spectral slope, SWA also changes during the night (decreasing, $F(3,96)=80.1$, $p<0.001$) and due to sleep deprivation (increasing; $F(1,32)=22.23$, $p<0.001$. Additionally, cycle effect remained significant when the full-night recordings in the cycle-count based groups were evaluated. As expected, lnSWA was markedly higher in the first cycle of RS compared to that in the first cycle of BS, and converged to similar levels by the end of the sleep episodes in both conditions (Figure 5)

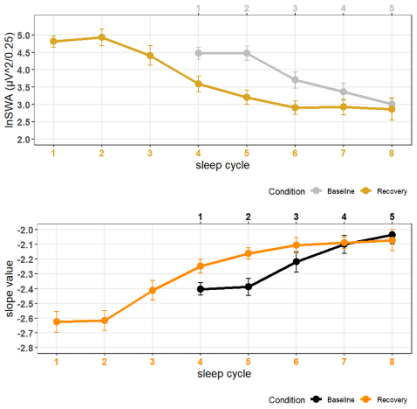

Figure 5. NREM sleep EEG SWA and spectral slope values in successive sleep cycles. Sample means and 95% confidence intervals are displayed in accordance with the phase advanced RS as compared to regularly timed BS (phase shift: approximately 3 sleep cycles).

4.2.3. Effect of sleep deprivation on spindle peak frequency

Although the analyses of the first 4 cycle revealed non-significant main effect of condition, which is in line with our hypothesis as we expected that sleep deprivation will not influence peak frequency (BS/RS: $F(1,27)=3.13$, $p=0.1$, cycle: $F(3,81)=3.27$, $p=0.025$), the separate analyses of the cycle count-based groups provided deeper insight into these effects. Sleep cycle has a significant effect in all groups, indicating U-shape-like dynamics of peak frequencies in both conditions (Figure 7). However, we estimated the timing of peak frequency minimum (nadir in sleep spindle frequency - NSSF) during sleep as we suggest that this can be considered a putative circadian phase indicator. Indeed, self-reported chronotype was reflected in the NSSF derived from baseline sleep, but not the NSSF derived from RS.

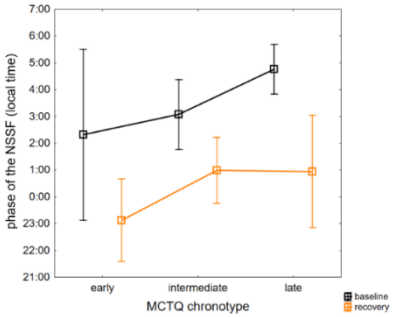

Figure 6. Difference in the phase of the peak frequency minima (NSSF) in RS and BS between MCTQ chronotype groups

Furthermore, we tested whether minimum peak frequency occurred around the same time of day during both BS and RS, thus we compared NSSF between the conditions. Contrary to our hypothesis, NSSF fell earlier in RS than in BS ($t(28)=5.7$, $p<0.0001$).

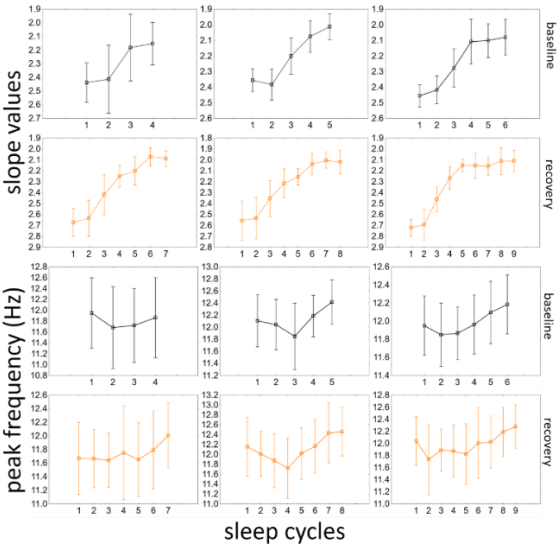

Figure 7. Overnight dynamics of slope values and peak frequencies in the different cycle count-based group

5. Conclusions

According to our results, the following conclusions can be drawn:

1. A proper distinction between the periodic and aperiodic components of the sleep EEG Fourier spectrum results in four physiologically and behaviourally meaningful metrics that efficiently characterize the known age-, sex- and IQ-correlates of the sleep EEG.
2. The largest peaks in the 9–18 Hz frequency range of NREM sleep EEG, as detected by our parametrization procedure in Study 1 and 2, effectively mirror spindles as they replicate topographical, sex-, age- and cognitive ability-related properties of sleep spindles.
3. The overnight dynamics of NREM sleep EEG spectral slope are similar to those of the gold-standard sleep homeostasis indicator, SWA. Furthermore, this measure has lower interindividual variability, suggesting its potential as an easily conceptualized reference value in future research and medical works.
4. The overnight dynamics of the peak frequency in the spindle range of NREM sleep EEG follow a U-shaped curve during habitual sleep, which has been associated with circadian modulation in other studies.
5. Sleep deprivation evidently induces changes in NREM sleep EEG spectral slope, leading to spectral steepening due to heightened sleep pressure. However, it also affects peak frequency and advances the time of its minimum in RS, which may indicate the entanglement of the two regulatory processes.

In sum, our results strongly support spectral slope as a reliable marker of sleep homeostasis, while promising about peak frequency. However, latter requires further research involving the direct manipulation of the circadian cycle to gain deeper insights.

6. Bibliography of the candidate's publications

Publications related to the thesis:

Bódizs, R., Szalárdy, O., **Horváth, C.**, Ujma, P. P., Gombos, F., Simor, P., Pótári, A., Zeising, M., Steiger, A., & Dresler, M. (2021). A set of composite, non-redundant EEG measures of NREM sleep based on the power law scaling of the Fourier spectrum. *Scientific Reports*, *11*(1), 2041. https://doi.org/10.1038/s41598-021-81230-7

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Publications not included in the thesis:

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