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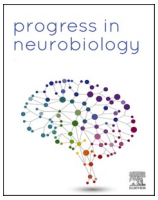

Fundamentals of sleep regulation: Model and benchmark values for fractal and oscillatory neurodynamics

Róbert Bódizs [a,*], Bence Schneider [a], Péter P. Ujma [a], Csenge G. Horváth [a], Martin Dresler [b], Yevgenia Rosenblum [b]

[a] Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary
[b] Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, the Netherlands

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ABSTRACT

Homeostatic, circadian and ultradian mechanisms play crucial roles in the regulation of sleep. Evidence suggests that ratios of low-to-high frequency power in the electroencephalogram (EEG) spectrum indicate the instantaneous level of sleep pressure, influenced by factors such as individual sleep-wake history, current sleep stage, age-related differences and brain topography characteristics. These effects are well captured and reflected in the spectral exponent, a composite measure of the constant low-to-high frequency ratio in the periodogram, which is scale-free and exhibits lower interindividual variability compared to slow wave activity, potentially serving as a suitable standardization and reference measure. Here we propose an index of sleep homeostasis based on the spectral exponent, reflecting the level of membrane hyperpolarization and/or network bistability in the central nervous system in humans. In addition, we advance the idea that the U-shaped overnight deceleration of oscillatory slow and fast sleep spindle frequencies marks the biological night, providing somnologists with an EEG-index of circadian sleep regulation. Evidence supporting this assertion comes from studies based on sleep replacement, forced desynchrony protocols and high-resolution analyses of sleep spindles. Finally, ultradian sleep regulatory mechanisms are indicated by the recurrent, abrupt shifts in dominant oscillatory frequencies, with spindle ranges signifying non-rapid eye movement and non-spindle oscillations – rapid eye movement phases of the sleep cycles. Reconsidering the indicators of fundamental sleep regulatory processes in the framework of the new Fractal and Oscillatory Adjustment Model (FOAM) offers an appealing opportunity to bridge the gap between the two-process model of sleep regulation and clinical somnology.

1. Introduction: measuring sleep by staging the polysomnographic records

Polysomnography, the gold standard method of measuring sleep relies on registering and analysis of time series reflecting ongoing brain electrodynamics, muscle tone, eye movement, heart rate, and respiration (Chokroverty et al., 2005; Rundo and Downey, 2019). Sleep-wake-related brain processes are most commonly assessed by analysing the scalp-recorded electroencephalogram (EEG), one of the key components of polysomnography, aiming to depict the time structure of summed, synchronized extracellular currents of cortical neurons (pyramidal cells organized along cortical columns), including synaptic currents, fast action potentials and their afterpotentials, calcium spikes and voltage-dependent intrinsic currents (Buzsáki et al., 2012; Jackson and Bolger, 2014). Other commonly recorded time series data in polysomnography recordings are the electro-oculogram (EOG) and the electromyogram (EMG) reflecting eye movements and muscle tone, respectively. Based on published expert consensual criteria, equidistant epochs of polysomnography records (20 or 30 s) are visually assessed by applying a set of written rules and categorized in different stages and then the whole record is characterized by the absolute or relative length and the pattern of succession of these sleep stages.

The first attempt to define such stages was based on the pioneering works of Alfred Lee Loomis. By relying largely on EEG records, Loomis defined the following sleep-wake stages: Alpha (A_L), Low voltage (B_L), Spindles (C_L), Spindles plus random (D_L), Random (E_L) (Loomis et al., 1937). (The subscript L, standing for Loomis, is added to the original capital letters in order to avoid confusion with other capital letter-based symbols and formulae). This qualitative description contains some objective frequency criteria in form of 14 Hz spindles and 0.5–3 Hz

* Correspondence to: Institute of Behavioural Sciences, Semmelweis University, Nagyvárad tér 4. H-1089, Budapest, Hungary.
E-mail address: bodizs.robert@med.semmelweis-univ.hu (R. Bódizs).

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random waves, as well as some amplitude specifications (20–40 μV spindles and random waves as high as 300 μV). However, random waves, which are termed nowadays slow or delta waves were not defined in terms of minimum acceptable amplitudes (Table 1).

The next consensual staging system was based on the work of Rechtschaffen and Kales (1968) (R&K), involving among others the illuminating lessons derived from the seminal discovery of the Rapid Eye Movement (REM) phase of sleep, as well as its recurrence in roughly 90 minutes cycles (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957). That is two phases of sleep were differentiated: non-REM (NREM) and REM sleep. The former was proposed to be further decomposed in Stages S1, S2, S3, and S4. S1 was defined as a transitional stage at the border of wakefulness and sleep (partially overlapping with stage B_L in the Loomis coding system), whereas S2 as stable NREM sleep with emerging sleep spindles and K-complexes, although of low depth (Loomis stage C_L). In turn, S3 and S4 (also termed together as slow wave sleep - SWS) are characterized by the presence of at least 20% or 50% of high amplitude (>75 μV peak-to-peak) slow waves (<2 Hz), respectively and are considered as deep sleep (Loomis stages D_L and E_L). In addition to low voltage fast EEG pattern with occasional theta, alpha and beta waves, the definition of REM sleep was linked to the presence of eye movement potentials as well (partial overlap with stage B_L in the Loomis system, Table 1). Recent criteria provided by the American Academy of Sleep Medicine (AASM) do not differentiate between Stages S3 and S4 sleep, considering them as a unitary stage in the context of the new terminology (Stages N1, N2, N3, and R, Fig. 1A). However, the criteria of the >75 μV peak-to-peak amplitude of slow waves was left unchanged, thus it is still actively used in scoring polysomnography records of sleep in adults (Berry et al., 2018; see Table 1 for further details).

Table 1
A shortened summary of rules for standard scoring of polysomnography: a historical and comparative account*.

Loomis**	R&K***		AASM****
A_L (alpha): Alpha rhythm (9–11 Hz) appearing in trains of various length. The eyes may be slowly rolling	Wake: The EEG contains alpha activity and/or low voltage, mixed frequency activity usually, but not necessarily accompanied by relatively high muscle tone, and often eye movements and blinks are present in the tracing		W: Trains of posterior dominant EEG alpha rhythm (8–13 Hz), eye blinks (0.5–2 Hz) or movements (initial deflection lasts < 500 ms)
B_L (low voltage): A quite straight record, with no alpha rhythm and only low voltage changes of potential. Rolling of the eyes may occur.	REM phase	REM: Relatively low voltage, mixed frequency EEG with episodic rapid eye movements, presence of sawtooth EEG waves, low muscular tonus	R: Low-amplitude, mixed-frequency EEG activity without K-complexes (lasting ≥ 0.5 s) and sleep spindles (11–16 Hz), sawtooth EEG pattern (triangular 2–6 Hz waves), low muscular tonus with transient irregular bursts (<0.25 s), rapid eye movements (initial deflection lasts < 500 ms)
	NREM phase	S1: Relatively low voltage, mixed frequency EEG with prominence of activity in the 2–7 Hz range (50–75 μV). Alpha activity < 50% of the record. Vertex sharp waves may occur. Slow eye movements, muscle tone: S1 < Wakefulness.	N1: Low-amplitude, mixed-frequency EEG activity (predominantly 4–7 Hz), alpha rhythm in less than 50% of the epoch, vertex sharp wave transients, slow eye movements (initial deflection lasts > 500 ms)
C_L (spindles): Line slightly irregular with 14 Hz spindles of 20–40 μV every few seconds.		S2: Presence of sleep spindles (12–14 Hz, duration ≥ 0.5 s) and K-complexes (duration ≥ 0.5 s, maximum: vertex) in the EEG	N2: presence of EEG transients like K-complexes (lasting ≥ 0.5 s) and/or sleep spindles (11–16 Hz)
D_L (spindles plus random): The spindles continue together with large random potentials 0.5–3 Hz. The random voltages may be as high as 300 μV.	SWS	S3: EEG waves of < 2 Hz frequency and > 75 μV peak-to-peak amplitude in 20–50% of the record	N3: EEG slow wave activity (0.5–2 Hz, >75 μV peak-to-peak) present in ≥ 20% of the epoch, optionally persisting sleep spindles
E_L (random): The spindles become inconspicuous, but the large random potentials persist and come from all parts of the cortex.		S4: EEG waves of < 2 Hz frequency and > 75 μV peak-to-peak amplitude in >50% of the record	

* Note the lack of objective amplitude criteria in many instances (rules; e.g.: "relatively low voltage")
** Loomis et al. (1937)
*** Rechtschaffen and Kales (1968)
**** American Academy of Sleep Medicine (Berry et al., 2018)

Although particularly important in the diagnosis and follow-up of several sleep disorders, polysomnography analysis techniques rely on a small fraction of the information available within the signals. A need to reconsider the current approach and extract more complex metrics to conform the needs of precision medicine were put forward (Lim et al., 2020). As Neil Stanley states, there is no perfectly staged sleep record(s) against which to benchmark human scorers or automatic scoring algorithms. A logical suggestion of the author is to change the way of approaching the issue of sleep staging: Instead of implementing consensual rules of the expert committees to computer programs, there is need to base the rules on objectively defined computer measures (Stanley, 2023). Here, we put forward an alternative concept of sleep based on the statistical regularities of time series and the parametrization of the EEG Fourier spectrum. Our intention is to transcend consensual staging rules and bridge the gap between the fundamental regulatory models and the clinical assessment of sleep.

2. Measuring sleep by spectral analysis of the EEG

2.1. Fourier analysis

The Fourier's theorem claims that any time series, irrespective of shape and complexity can be decomposed to regular sine and cosine waves of varying frequencies, phases and amplitudes. The process of this decomposition is known as Fourier analysis, which results in a set of coefficients forming complex numbers. The modulus of these complex numbers is an array of amplitudes of component waves (harmonics) as a function of frequency and called the amplitude spectrum (i.e. spectrum of frequencies, see Fig. 1B), whereas the sets of squared amplitudes or areas below the squared harmonic waves are known as power spectrum or power spectrum density, respectively. The squared spectra are also termed as periodograms (Cox and Fell, 2020; Rampil, 1998).

2.2. Pioneering Fourier analysis studies of EEG: conclusions are still highly relevant today

The first published Fourier analyses of EEG time series is a German-language paper emphasizing the presence of several harmonics in the EEG, suggesting the need to consider the potential role of other frequencies, besides alpha and beta waves primarily known at that times (Dietsch, 1932). A few years later a mechanical-electrical integrator was designed by Albert M. Grass and used in a seminal work in the field. The

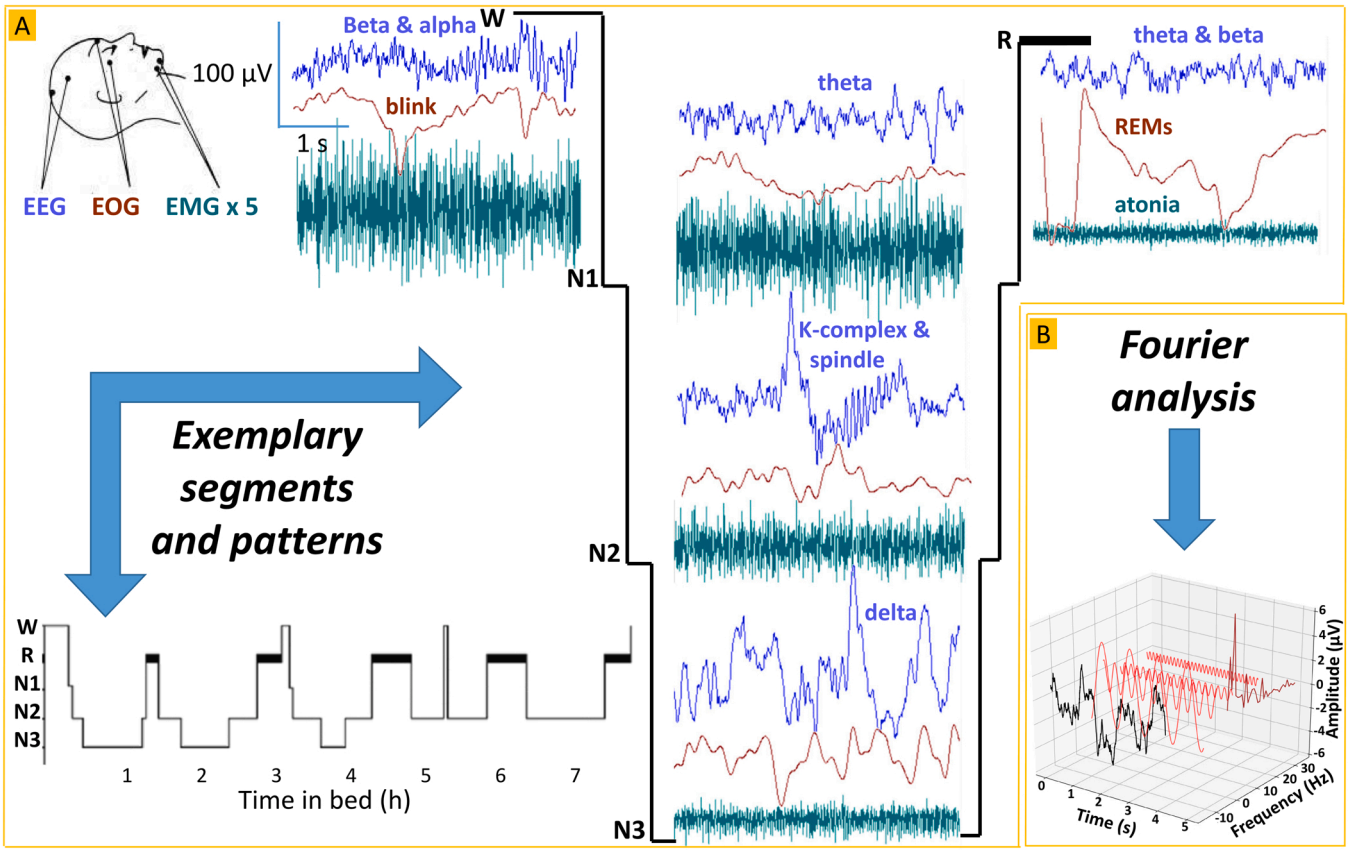


Fig. 1. Exemplary segments from a visually scored polysomnography record and the depiction of Fourier analysis. A. Hypnogram, as well as EEG, EOG, and EMG traces of a healthy adult male (age: 33 years), with samples taken from various sleep stages according to the AASM criteria. REMs – rapid eye movements. B. Fourier analysis of EEG time series depicted on a segment of human scalp EEG record (black). Red sinusoid waves of different frequency, amplitude and phase are examples for harmonics derived from Fourier analysis. Summation of all harmonics results in the original time series, whereas their amplitude along the frequency scale is the amplitude spectrum (dark red). That is Fourier analysis transform the data from the time domain (black) to the frequency domain (dark red).

motivation of this second investigation is still highly relevant in the 21st century sleep science: "The electroencephalogram as usually recorded shows a confusion of wave forms and a mixture of frequencies which are impossible of accurate visual analysis. With experience one can learn to detect certain gross features which have significant clinical and physiological correlates, but in this there is more art than science. Certain crude indices which have been devised as a basis for comparison are open to theoretical criticism. *They are not arrived at objectively, and do not afford a consistent expression for the data*" (Grass and Gibbs, 1938; emphasis added). The study depicts several examples of non-linear decrease in the amplitude spectra, transiently overridden by peaks emerging around the frequencies in the alpha and/or theta range, cohering with the current knowledge on the spectral features of resting state EEG. Fourier transforms of the EEG during sleep were first reported by Knott et al. (1942) leading the authors to conclude that the traditional categories of sleep (Loomis et al., 1937) do not take into account all of the phenomena appearing on the record. In addition, sleep was revealed to differ "from the waking state solely in the *distribution of energy throughout the continuum of frequencies*, not in the introduction of new frequencies" (Knott et al., 1942; emphasis added). In sum, the inherently suboptimal effectivity of visual EEG analysis and the characterization of sleep-wake states as a pattern of energy distribution over the frequency continuum are two conclusions with outstanding relevance for our current attempts to deliberately describe the fundamental sleep regulatory processes.

2.3. Band-limited and binwise spectral studies of sleep-wake EEG

The vast majority of objective and quantified EEG data in the field of sleep research are derived from the Fast Fourier Transformation (FFT)-based analysis of short and tapered record segments of equal length, the squared modulus of which are averaged over longer periods (multiple segments), according to the Welch-procedure (Welch, 1967). Commonly used EEG spectral power (density) measures are band-limited, according to the canonical frequency boundaries, expressed as integrals over the relevant portion of the spectrum or binwise, reflecting the amplitude or energy of narrow (e.g. 1 Hz wide) frequency constituents (Campbell, 2009), sometimes limited by the individual harmonics (the reciprocal of the segment length, e.g. 0.25 Hz in case of 4 s segments; (Cajochen et al., 1999). These EEG-indices are commonly used in depicting sleep quality, depth, as well as its basic regulatory processes. In the next sections new insights and new avenues in unravelling the basic sleep regulatory processes by spectral EEG analysis will be presented. The aim of the present paper is to reframe the field and provide mathematically precise, non-redundant measures of basic sleep regulatory processes, which are appropriate for benchmarking and translation.

3. Basic sleep regulatory processes: sleep homeostasis

3.1. Basic concepts of homeostasis and their applicability to sleep

Generally accepted criteria for homeostatic regulation are the existence of a regulated variable (e.g. blood glucose concentration), a normal range or value (e.g. 70–110 mg/dl for glucose), a sensor sensing the deviation from the normal range (e.g. chemosensors in the hypothalamus/pancreas), a control center (e.g. hypothalamus), effectors (e.g. liver, adipose tissue, and skeletal muscle), as well as effector response (e.g. alter storage/metabolism/release of glucose and its related

compounds) (Modell et al., 2015). In addition, the concept of homeostasis should be approached in behavioural terms involving appetitive and consummative responses, the latter referring to active searching processes indicative of desire and the final response directed toward achieving a goal, respectively. These behavioural phenomena are known to be initiated in conditions of departing from the so-called set points, that is the physiological values around which the normal range of the regulated variable fluctuates (e.g. 37 °C in case of core body temperature).

Any regulated variable or index assumed to be involved in or just reflecting the process of sleep homeostasis should depend on the amount and/or intensity of wakefulness and sleep of the organism. In practice this means a progressive change during wakefulness and sleep, where the changes measured during the two states are characterized by opposite signs. In addition, a challenge of the sleep homeostat by sleep deprivation is expected to induce a rebound change during subsequent recovery sleep. The hypothesized regulated variables involved in sleep homeostasis commonly consists of the accumulation and decomposition of various hypothetical, hypnogenic molecular factors during wakefulness and/or sleep (Borbély and Tobler, 1989), including adenosine, the breakdown molecule of ATP (Porkka-Heiskanen et al., 1997), as well as newer candidate factors, like metabolic waste (Xie et al., 2013), protein fragments (Varshavsky, 2019), and endozepines (Sher et al., 2021). Moreover, the use-dependent release of somnogenic cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) by glial cells (Krueger et al., 2008) or the learning/plasticity-related production of the neurotrophin brain-derived neurotrophic factor (BDNF) (Faraguna et al., 2008), all acting in a paracrine mode, are further potential regulated variables. Besides the fact that these assumptions need further empirical support, there is no available information on the normal range/set point of the above mentioned molecular factors. A parsimonious and biologically realistic framework is that no single neurotransmitter or neuromodulator, but rather their complex interactions within organized neuronal ensembles, regulate waking and sleep states (Holst and Landolt, 2022). Sleep pressure was shown to be reflected in terms of theta EEG activity during wakefulness of human subjects (Finelli et al., 2000; Snipes et al., 2022) and rats (Vyazovskiy and Tobler, 2005), but again, no set point for resting state theta EEG power was ever established. The deviation of one or more of the above (or other as yet undetermined) regulated variables from the assumed normal value is sensed by specific receptors, which would then trigger the control centre, presumably located within the ventrolateral preoptic area of the hypothalamus (Arrigoni and Fuller, 2022), and initiate the appetitive behaviour, which is in fact sleepiness and sleep-preparatory behaviour, including resting, eye closure and the search for sleep places (Axelsson et al., 2020). Once initiated, sleep can be considered as a consummative behaviour (c.f. eating), serving specific functions fulfilled by the effector organ, the central nervous system and its effector responses, the latter involving sleep-state specific neural activities. Functions fulfilled by sleep overlap in part with the ones we can derive from the hypothesized regulated variables, such as removal of metabolic waste (Xie et al., 2013) and protein fragments (Varshavsky, 2019), conservation of synaptic infrastructure (Krueger and Obal, 2003) or the renormalization of synaptic strengths (Tononi and Cirelli, 2003, 2014).

Given the scarcity of knowledge on the regulated variables in the sleep domain, as well as the excellent homeostatic behaviour of sleep EEG slow waves, the currently approved concepts and models of sleep homeostasis rely largely on the intensity of the effector response (i.e. sleep intensity). According to the widely acknowledged terminology, sleep homeostasis refers to the continuous accumulation of sleep propensity in the absence of sleep, as well as its decay during the ongoing sleep process. Indeed, several measures and sleep features were shown to reflect sleep-wake history. Known indices of sleep depth or enhanced sleep need are increases in sensory thresholds during sleep (Blake and Gerard, 1937), SWS amount (Knowles et al., 1986; Webb and Agnew, 1971), spectral power of EEG slow wave activity (SWA: 0.75–4.5 Hz; Achermann et al., 1993; Borbély, 2001), the amplitude, the slope and the frequency of individual sleep slow waves/oscillatory cycles, as well as a lower number of multi-peak slow waves (Bersagliere and Achermann, 2010; Riedner et al., 2007).

Although, the characterization and modelling of sleep homeostasis by relying on the effector response of the process seems non-appropriate at the first sight, this approach might have its own strengths and supports. As an analogy, we could consider feeding behaviour. Specifically, activity of lateral hypothalamic neurons producing melanin-concentrating hormone (MCH) increases in response to food-predictive cues and is correlated with food-motivated responses (indexing the appetitive response). In addition, MCH neuron activity is increased during eating per se, and this response is highly predictive of caloric consumption and declines throughout a meal (consummatory phase) (Subramanian et al., 2023). This example suggests that the appropriate measures of the key elements of precise neural regulatory processes of feeding behaviour provide us with a feasible model of the homeostatic process. As an analogy, we can say that the appropriate indexing of the key elements of the neural processes involved in sleep homeostasis, could provide us with a model describing sleepiness (appetitive behaviour), sleep initiation (start of the consummative behaviour), as well as sleep intensity (as an analogy of caloric consumption) and its decrease (c.f. decline of MCH neuron activity throughout a meal).

Indeed, such models were built and well-known in sleep research. The two-process model of sleep regulation posits that the homeostatic process (Process S) is indexed by sleep EEG SWA, reflecting sleep intensity, tracking sleep-wake history, especially the decline throughout sleep and rebounds after extended periods of sleep loss (Borbély et al., 2016; Borbély, 1982). One significant drawback of this type of modelling is indeed related to the lack of the normal range of values. Is there a chance to find a normal range of values in terms of the effector response, instead of the largely unavailable regulated variable? A further question we focus on in this paper is the following: are slow EEG waves or their canonical spectral measures specific in depicting sleep homeostasis? In order to provide a deliberate analysis of these issues, the literature on the human EEG spectral power indexes of individual sleep-wake history, current sleep stage, age-related differences and brain topography-characteristics is reviewed. The major findings of the literature are then reframed in the context of the spectral exponent, a constant ratio of lower-to-higher frequency power.

The core electrophysiological features of sleep wake-states of different mammalian and avian species overlap in a considerable way, the behavioural quiescence and increased sensory thresholds being hallmarked by high amplitude, low frequency EEG patterns (slow or delta waves) (Van Der Meij et al., 2019). Nevertheless, some birds and cetaceans are known for typical fluctuations in different indirect measures of assumed sleep need (Rattenborg et al., 2016; Van Hasselt et al., 2021, 2023). Along with other species-specific sleep traits this point constitutes a challenge for our attempts to conceptualize a universal framework for the regulation of sleep. In order to provide a more general perspective of our claims, we will return to this point in a specific subheading devoted to the comparative and ecological aspects of the fundamental sleep regulatory processes reconceptualized herein.

3.2. Indexing sleep homeostasis: looking beyond the slow wave/delta EEG activity

3.2.1. Sleep EEG spectral power as an index of sleep-wake history

Dynamical changes in sleep EEG SWA or delta (1–4 Hz) power compared to the individual-specific reference values were shown to index sleep-wake history with high precision, the former being considered as a primary marker of sleep homeostasis (Achermann et al., 1993; Borbély, 2001). Moreover, EEG slow waves are the epitome of deep NREM sleep (Borbély, 2001). Indeed, detailed analyses of the spectral features/frequency composition of the EEG signal in terms of sleep homeostasis suggest that the canonical low frequencies (delta or SWA) are

not exclusive in terms of indexing sleep-wake history. The earliest available empirical evidence based on the spectral analysis revealed that EEG frequency components up to 8 Hz are enhanced during recovery sleep after sleep deprivation (challenges of the sleep homeostat) as compared to baseline sleep (Borbély et al., 1981), but the contribution of higher frequencies seem to provide us with a diminishing return: the higher the EEG frequency, the lower its involvement in sleep homeostasis. In other words, excess power during recovery sleep levels off with increasing frequencies. Similar findings were reported in several follow-up studies. Recovery sleep after acute slow wave or total sleep deprivation in adult volunteers was shown to be characterized by increases in NREM phase delta, theta and occasionally alpha EEG power in many reports, but excess power declined as a function of increasing frequency (Cajochen et al., 1999, 2019; Dijk et al., 1990; Dijk and Beersma, 1989; Ferrara et al., 2002; Finelli et al., 2001; Marzano et al., 2010). Findings derived from experimental manipulations mimicking chronic sleep deprivation by settings involving repeated sleep restriction interventions revealed that NREM sleep EEG power changes extend over the theta range (1.25–7.25 Hz) (Åkerstedt et al., 2009), whereas the frequency gradient of excess power in the conditions of elevated sleep pressure is characterized by a gradual levelling off (Brunner et al., 1990, 1993). In addition, the systematic control of pre-sleep wakefulness in nap studies revealed a similar pattern. Increased amount of wakefulness was followed by increased nap sleep EEG power in the 0.25–8 Hz range, that is far over the upper limit of SWA, but the wake time-dependency progressively dampened within this array of frequencies (Dijk et al., 1987). Last, but not least the reduction of night time sleep pressure by an experimentally scheduled early evening nap consistently decreased NREM sleep EEG power in an extended range encompassing the delta, theta and alpha frequencies during the first three NREM-REM cycles. Maximal decrease emerged in the 1–2 Hz bins, whereas the successive ones were characterized by a frequency-dependent, progressive dampening in their effectivity of reflecting the nap-related reduction of sleep pressure (Werth et al., 1996). Given their pivotal role in indexing sleep-wake history, delta (1–4 Hz) and theta (4–8 Hz) EEG were explicitly termed as “homeostatic frequencies” by several authors publishing in this field (Campbell and Feinberg, 2009).

The dissipation of sleep need during the course of night sleep was shown to be paralleled by a declining trend of power density in the 0.25–12 Hz range over the first four NREM sleep episodes. Again, this finding coheres with the above mentioned involvement of theta and perhaps alpha frequency ranges in sleep homeostasis (in addition to the well-known delta or SWA frequencies). Furthermore, researchers report a progressive dampening in the rate of overnight decline in NREM sleep EEG power values with increasing frequencies within the 0.25–12 Hz range (Aeschbach and Borbély, 1993). Power in higher frequency bins (closer to the 12 Hz upper limit) followed a flatter overnight decay, perhaps suggesting a reduced sleep-time-dependent dampening. This pattern is evident, although usually not emphasized in other studies analysing the changes in NREM sleep EEG power in successive sleep cycles of healthy adults (Dijk et al., 1990; Werth et al., 1997) and adolescents (Jenni and Carskadon, 2004). Similar findings were reported by reliance on band-limited spectral power analysis: overnight declines are most expressed in SWA, but present in theta (4–7.75 Hz) and alpha (8–12 Hz) power as well. The higher the frequency range, the lower rate in its overnight decrease or dependence on pre-sleep wakefulness is seen (SWA > theta > alpha; (Gaudreau et al., 2001; Münch et al., 2010)).

Besides the delta and theta/alpha frequency EEG activities positively indicating increased sleep depth (intensity), several studies admit sigma, beta and/or gamma activity as its potential negative correlate. Specifically, one study reported reductions in average-referenced EEG beta power in recovery sleep after sleep deprivation. Thus, the experimental challenge of the homeostat by sleep deprivation resulted in the well-studied enhancement of NREM sleep EEG power in the lower frequency ranges (0.75–10.5 Hz) paralleled by reduction in the ranges of 12–12.25 Hz and 13.25–25 Hz (Finelli et al., 2001). Other findings indicate a reliable negative correlation between overnight changes in sleep EEG delta (0.3–3 Hz) and beta (20–28 Hz) power in all subjects (Uchida et al., 1992). In addition, sleep EEG spectral power at several frequency bins in the beta/gamma range was shown to increase during the fourth as compared to the first NREM period in healthy adult volunteers (Mukai et al., 2003), which is a further indirect support for the idea that increases in beta and gamma EEG activity might indeed index the dissipation of sleep need in humans.

The above findings indicating a preponderance of low EEG frequencies in indexing sleep-wake history, but the diminishing return obtained by focusing on higher bins or ranges, implicitly suggest that the power ratio of lower-to-higher frequencies reflects sleep homeostasis: the higher the homeostatic pressure the higher the ratio of lower over higher frequency components in the EEG. This assumption coheres with findings suggesting the usefulness of different ratios of band-limited spectral EEG power in the automatic recognition of R&K or AASM sleep stages in humans (Krakovská and Mezeiová, 2011; Reed et al., 2017).

3.2.2. *Sleep EEG spectral power as an index of sleep stages*

Given the fact, that the architecture of sleep is in itself a reflection of sleep homeostasis, with SWS (S3 and S4) or N3 considered as intense sleep (Knowles et al., 1986; Webb, 1989; Webb and Agnew, 1971), the comparison of the spectral characteristics of sleep stages might be conceived as proxies of sleep-wake history. Comparison of sleep stages scored on the basis of the R&K criteria in terms of power spectral density of the EEG records resulted in a pattern of frequency-dependent gradient, which is similar to the one detected in terms of the effect of sleep-wake history. That is, maximal between stage differences are seen in the lowest frequency range (0–2 Hz: S4 > S3 > S2 > REM > S1 > W). Moreover, increasing frequencies are characterized by decreasing stage differences, reaching the between stage equality in the 8–10 Hz alpha band. Authors of this study added that "not only was the maximal power found in the slowest spectrum component of stage 4, but also the minimal power in the highest part of the spectrum of stage 4." Slowest and highest parts of the spectrum were 0–2 and 22–30 Hz, respectively (Dumermuth et al., 1983). Thus, if we consider sleep intensity or sleep depth on the basis of pre-defined consensual criteria and expert rule-based scoring anchored primarily to the presence of high amplitude, low frequency (<2 Hz) waves (see the R&K criteria for S3 and S4 stages), the phenomenon of frequency-dependent diminishing returns emerges in a similar range (1–10 Hz), echoing the already presented patterns of excess power in recovery sleep and overnight decay rates. Moreover, an index of sleep “shallowness” is emerging in higher frequency ranges. Similar power gradients were reported for the difference between NREM and REM or R&K S2–S4 and S1 sleep EEG (Aeschbach and Borbély, 1993; Werth et al., 1997). As regarding NREM-REM differences, power in the delta (0.25–4.5 Hz), theta (4.75–8 Hz) and sigma (11.25–15 Hz) band in all derivations was higher, whereas power in the beta band (15.25–25 Hz) was lower in NREM sleep than in REM sleep (Werth et al., 1997).

These data suggest that differences in sleep stages are found in spectral power at multiple EEG frequencies, but maximal effects are found in the slowest ranges, whereas the higher ones are characterized by progressively decreasing differences. In addition, the order of stage differences is inverted at the higher frequency (beta) range of the spectrum.

3.2.3. *Sleep EEG spectral power as an index of development and aging*

Several findings on the maturation and aging of sleep provide indirect support for the assumption of the diminishing returns in the measurement of sleep homeostasis by increasing the EEG frequencies. In order to unravel these evidences we have to consider the fact that the percentage of SWS, an architectural proxy of sleep intensity, is significantly negatively correlated with age (5–102 years) (Ohayon et al., 2004). Indeed, the maturational decrease in NREM sleep EEG delta

(1–4 Hz) power is paralleled by similar, albeit lower rate of developmental reduction in theta activity (4–8 Hz) between 6 and 18 years of age (Feinberg and Campbell, 2013). Again, this indirect evidence suggests that EEG SWA/delta most distinctly prevails over theta activity in younger subjects when sleep was found to be deeper in architectural terms.

A negative frequency gradient of excess power in younger as compared to older subjects was reported in several studies (Dijk, Beersma, and van den Hoofdakker, 1989; Gaudreau et al., 2001). In addition, the higher delta and theta (0.25–8 Hz) NREM sleep EEG power in younger as compared to older subjects was paralleled by lower beta frequency (18.25–32 Hz) activity in the night sleep records of the participants (Carrier et al., 2001). Both effects (increased low and decreased high frequency activities in younger subjects) were characterized by a statistically significant dampening during the successive NREM sleep periods, indicating the involvement of sleep homeostasis in the age-related effects. The reversal of the age-effects in the beta as compared to the delta and theta ranges in earlier NREM sleep periods suggests that SWA is not the only marker of age-related sleep EEG power differences and the overall pattern coheres with the concept of the frequency-dependent diminishing returns.

3.2.4. *Sleep EEG spectral power as an index of regional differences in sleep homeostasis*

The hypothesis on the intimate relationship between human SWS and the prefrontal cortex was put forward on the basis of mostly indirect evidence by J. A. Horne (1993). A notable early report on the frontal predominance of SWS delta (2.1–5 Hz) EEG activity might be considered as a pioneering study revealing this type of topographical pattern (Buchsbaum et al., 1982). A significant quote regarding delta (2.1–5 Hz) power states: “anterior and central midline values tripled from awake to stage 4, whereas occipital and temporal power merely doubled” (Buchsbaum et al., 1982). Later analyses focusing on the region-specific EEG power revealed "a specific involvement of frontal parts of the cortex in sleep homeostasis. The regional differences in sleep EEG spectra indicate that sleep is not only a global phenomenon but also a local brain process with a different regional involvement of neuronal populations" (Werth et al., 1997). Spectral analysis revealed a consistent frontal predominance of SWA in adult subjects, and excess SWA in recovery sleep after sleep deprivation is most pronounced in frontal areas (Cajochen et al., 1999; Finelli et al., 2001; Marzano et al., 2010; Rusterholz and Achermann, 2011). Fronto-central over centro-parietal ratios of bipolarly referenced NREM sleep EEG spectra indicate the anterior dominance of the 0–2 Hz activity and a shift to a posterior dominance at higher frequencies, with the exception of spindle frequency activity (Werth et al., 1997).

In sum, available data indicate that heightened sleep pressure associates with a negative frequency gradient of excess sleep EEG power, whereas the opposite is seen in terms of retained power in conditions of lowered sleep pressure. This claim got empirical support in terms of sleep pressure differences related to sleep-wake history, sleep stages, development and aging, as well as fronto-posterior localization. In addition, these frequency gradients extend far beyond the SWA or delta ranges, suggesting that these band-limited power values are not exclusive in tracking sleep pressure.

3.3. *The issue of appropriate reference values for SWS/N3 and/or sleep EEG SWA/delta power*

Several independent datasets and analyses suggest that the sleep intensity measures based on EEG slow waves are largely individual-specific, stable in time (trait-like), and consequently inappropriate for deriving reference values (ranges defining “normal” or healthy sleep).

Wilse B. Webb, the leading scientist of the first series of systematic investigations revealing the dependence of SWS or R&K Stage 4 sleep on sleep-wake history, noted that around 81% of the variance in Stage 4 time is determined by stable interindividual differences (Webb, 1989). Later studies revealed similar findings, as well as a repeatedly expressed objection in defining reference values for normal sleep, which would be of particular relevance for somnologists. A study based on the data of 206 healthy adults aged from 19 to 73 years concluded that the informative value of sleep reference data in healthy individuals is limited because of high interindividual variation within sleep variables, including percentages of N3 sleep and EEG power spectral measures (Hertenstein et al., 2018). Although a large meta-analytic study involving several former investigations reported age- and sex-specific reference values for sleep architecture, but not spectral EEG variables (Boulos et al., 2019), it is still highly challenging to handle the large interindividual differences reported in this paper. A good example for this type of problem is the reported average of 18.1% of N3 sleep in 50–64 years old subjects with a 95% prediction interval of 2.5–33.7%. That is, two subjects of let us say equal age of 57 years with N3 percent of 3 and 33 have to be considered as sleeping equally well and normal, although the former value is close to 0 (meaning almost no deep sleep at all), whereas the latter indicates amounts matching the average of prepubertal children (Scholle et al., 2011), known to be characterized by the highest N3 levels among all age groups. New reports of similar benchmarking analyses performed on a Korean population resulted in similar findings (Yoon et al., 2021).

The analysis of nocturnal sleep and daytime naps revealed consistent, trait-like interindividual differences in SWS even after controlling for prior sleep-wake history leading the authors to conclude that the attempts to define “normal” sleep architecture in both clinical and experimental settings face severe problems (Gander et al., 2010). Last, but not least Tucker and colleagues noted that: “…for non-REM delta power – a putative marker of sleep homeostasis – the interindividual differences were from 9.9 to 12.8 times greater than the group-average increase following sleep deprivation relative to baseline” (Tucker et al., 2007). The ubiquity of large interindividual differences reported in this ground-breaking observation haunts all attempts to define reference values in sleep EEG power. Using relative instead of absolute spectral power (Yoon et al., 2021) does not seem to resolve the issue, as non-delta ranges reflect primarily the reciprocal values of delta (Cox and Fell, 2020), thus cannot fully control the inherent scaling problem in the field.

Despite the significant trait-like interindividual variability outlined above, a recent paper presented empirical age norms for the sleep EEG across the lifespan from 11 days to 80 years. Variables include log-normalized, band-limited absolute and relative spectral power stratified by sex. Stage N3 relative delta power of patients suffering from Alzheimer’s disease or depression was shown to be lower than the reference (Sun et al., 2023). The potential utility of these age-norm measures in determining healthy sleep and optimal sleep pressure has to be explored in future studies.

The scarcity of appropriate reference values in sleep EEG spectra caused a long-lasting translational gap in the field of sleep science. Well-elaborated and precise sleep regulatory models are seldom used in clinical sleep science or in defining the quality of sleep. Measuring delta power or SWA are particularly useful in predicting their own changes, but not appropriate to compare recordings from different subjects. Below we suggest an alternative approach based on the spectral exponent (slope) which we hypothesize to bridge this gap and provide the sleep scientists and clinicians with a standardisable measure expressing the constant ratio of lower over higher frequency EEG spectral power.

3.4. *Low frequency sleep EEG power reflects alternating up and down states (bistability)*

After analysing the basic phenomenological features of NREM sleep EEG slow waves detected by filtering and amplitude threshold-based criterion, Bersagliere and Achermann (2010) concluded that increased sleep pressure during recovery sleep after prolonged wakefulness results

in faster alternations between depolarized up- and hyperpolarized down-states at the cellular level. In addition to the increase in frequency and slope of NREM sleep EEG slow waves a decrease in multi-peak waves was reported in this study. In addition, amplitudes of slow waves were also elevated during recovery as compared to baseline sleep. Accelerated up-down state alternation together with a reduction in multi-peak waves are suggestive of network bistability. Moreover, authors conclude that findings do not question SWA as a marker of sleep homeostasis, as the observed changes occurred within the same frequency range.

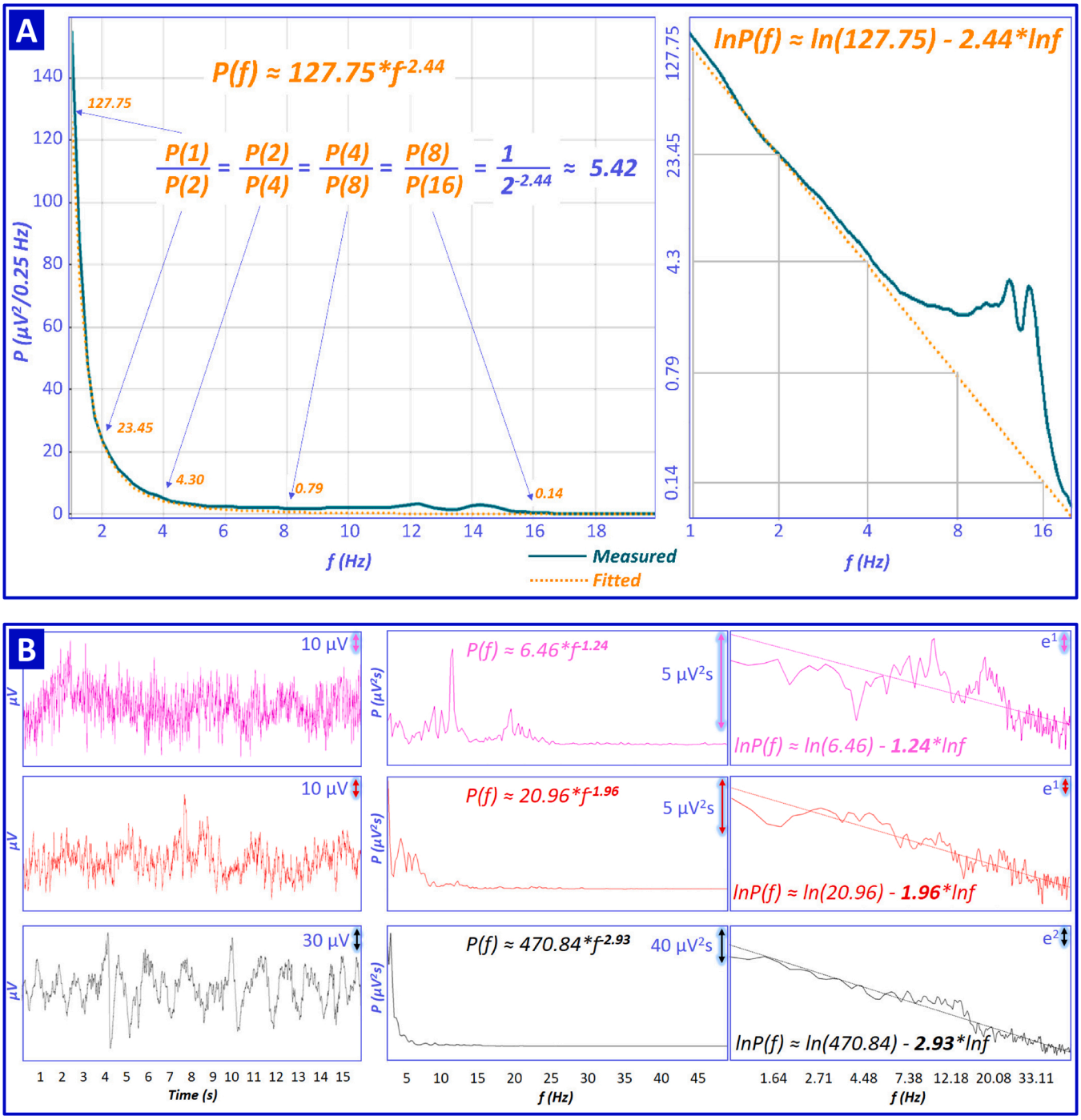


Fig. 2. Spectral power ratios, power laws, spectral exponents and the colours of noise. A. The spectral exponent is a measure of the constant ratio of lower and higher frequency EEG power and can be linearized in double logarithmic coordinates. Teal: whole-night NREM sleep EEG power spectral density function derived from the right central recording location C4 (reference: mathematically-linked mastoids, sampling rate: 249 Hz, mixed-radix FFT routine, 4 s Han window, 50% overlap, subject: healthy female of 27 years of age). Orange dotted line: fitted power law function according to the $P(f) = Cf^{\alpha}$ formula (see the actual fitting equation in orange on the top of the figure). Power ratios derived from the division of lower with higher frequency bin power values in the fitted function result in constant values depending on the multiplier defining the distance between lower and higher frequencies and the spectral exponent (-2.44 in this case). B. Different spectral exponents define different types of EEG time series. Examples for EEG time series recorded in wakefulness, wake-sleep transition period and N3 sleep approximating so-called pink, red (also known as Brownian) and black -noise, respectively (healthy human male volunteer, age: 20 years).

3.5. Low frequency sleep EEG power reflects the hyperpolarization of thalamocortical and cortical neurons

Neuronal membrane hyperpolarization is a critical factor in the emergence of low frequency EEG components during sleep. First, the advanced hyperpolarization of thalamocortical neurons during late NREM sleep results in the appearance of delta (1–4 Hz) oscillations in thalamocortical assemblies. Furthermore, these assemblies are partially synchronized by widespread depolarizations separated by long-lasting hyperpolarizations (cycle length $\geq$ 1 s), both generated in the cortex (Steriade et al., 1993). The latter are frequently called as cortical up and down states, respectively. As a consequence, the net increase in both thalamic and cortical hyperpolarization seems to be a crucial factor in understanding the neurophysiological bases of EEG slow wave activity.

Additional evidence suggests the contribution of other mechanisms to the emergence of EEG slowing in states characterized by decreased thalamocortical membrane depolarization. A specialized subset of thalamocortical neurons interconnected by gap junctions were shown to exhibit high threshold burst firing in the range of 2–13 Hz, with the precise frequency increasing with increasing depolarization. As a consequence, the same cellular components that underlie thalamic alpha rhythms can also lead to theta (2–7 Hz) rhythms when the thalamocortical neuron population is less depolarized in early sleep periods (Hughes and Crunelli, 2005).

4. The spectral exponent and sleep homeostasis

4.1. History and definition of the EEG spectral exponent

4.1.1. A constant ratio of lower/higher frequency power in sleep EEG

First reports on the differential analysis of the overall declining trend and the peaks in the EEG power spectra relied on semilogarithmic plots (logarithm of power as a function of frequency) and can be considered now as forerunners of the spectral exponent or spectral slope-based approaches in electrophysiology (Dumermuth et al., 1977; Matthis et al., 1981). Indeed, current approaches are explicit in emphasizing the importance of the constant ratio of lower over higher frequency EEG spectral power as measured by Fourier-analysis. This ratio is elegantly synthesized in the compact measure called spectral exponent. The concept is based on the idea that the power spectral density (P) of the human EEG follows a power law-type distribution (Pritchard, 1992), depending on the exponents (α) of the frequency (f) and a constant multiplier (C), but containing a peak power (PPeak) function as well (Bódizs et al., 2021; Lázár et al., 2022):

$$P(f) = Cf^{\alpha}P_{Peak}(f) \quad (1)$$

If we consider the power law function, assuming that there are no spectral peaks or that the peaks were removed (PPeak(f) = 1), the ratio of power at frequency f and power at a higher frequency k×f, where k is a positive real number, results in a constant (Fig. 2A):

$$\frac{P(f)}{P(kf)} = \frac{Cf^{\alpha}}{Ck^{\alpha}f^{\alpha}} = \frac{1}{k^{\alpha}} \quad (2)$$

Thus, the ratio of lower/higher power is invariable, depending only on the distance chosen between the power bins (k) and the spectral exponent (α). Evidence presented in the former subheadings suggests the utmost importance of measuring power ratio in depicting sleep homeostasis. Accordingly, definitive evidence suggests that studies relying on EEG frequency band ratio measures reported in part the implicit involvement of the power law scaling or the spectral exponent in differentiating sleep stages (Donoghue et al., 2020). Moreover, pioneering studies aiming to characterize the fractal structure of human EEG or automatize the R&K sleep scoring system revealed that the spectral exponent of the EEG is among the most reliable measures of sleep stage classifiers (Krakovská and Mezeiová, 2011; Pereda et al., 1998).

4.1.2. The spectral slope is equivalent with the spectral exponent

Power law spectra can be linearized by its transformation to a function in double logarithmic coordinates (logarithm of power as a function of the logarithm of frequency, Fig. 2). This results in a linear decay in the log-transformed EEG power spectra as a function of the log-transformed frequency, changing the spectral exponent to a spectral slope (Bódizs et al., 2021):

$$\ln P(f) = \ln C + \alpha \ln f + \ln P_{Peak}(f) \quad (3)$$

The spectral slope is equal with the spectral exponent in this type of mathematical parametrization of the periodogram, whereas the natural logarithm of the constant multiplier becomes the intercept of the linear function. Natural instead of 10-based logarithm is used because of the assumed natural logarithmic relationship between brain oscillators (Penttonen and Buzsáki, 2003).

Due to the fact that damping is a common feature in physical systems, a broad class of real-world signals have a high-frequency slope, but a plateau in the vicinity of zero frequency (also known as Matérn process; (Lilly et al., 2017)). As a consequence, the low-frequency limit of the validity of Eqs. (1) and (3), has to be considered by focusing on the appropriate frequency range or by explicit modelling of the low frequency plateau by the inclusion of the so-called spectral knee-parameter in the equation (Donoghue et al., 2020). The low frequency spectral knee of the EEG or LFP signals could vary as a function of high-pass filtering of the EEG recording device, the multifractality of neuronal processes or perhaps even brain size.

The fact that EEG spectra can be reliably approximated by a power law function indicates that band power-type measures are inherently redundant metrics. Band power values express in fact the manifestations of the same underlying statistical regularity at different frequency domains. But band power values conflate the power law function with the spectral peaks indicating specific oscillatory phenomena (Donoghue et al., 2020). The spectral exponent/slope is an indicator of aperiodic, scale-free activity, in contrast with oscillatory activity characterized by specific periods (wavelengths) and scales. That is, the first type of activity is stochastic (c.f. the term “random activity” introduced by Loomis et al. (1937), whereas the latter is highly predictable (e.g. sleep spindle oscillations).

4.1.3. Modelling the diminishing return by the EEG spectral exponent

By assuming that the spectral exponent of the EEG is an index of sleep homeostasis, the frequency-dependent diminishing return can be modelled with mathematical confidence. The ratio of two power laws P1 (f) and P2(f) expressing two different levels of sleep pressure results in a power law with an exponent equalling the difference between the exponents of the original functions (n).

$$\frac{P_1(f)}{P_2(f)} = \frac{C_1 f^{\alpha}}{C_2 f^{\alpha+n}} = \frac{C_1}{C_2} f^{-n} \quad (4)$$

Usual values for the spectral exponent α vary between −1 and −4 (Freeman and Zhai, 2009). In case if the denominator, which is P2(f) in this example is a flatter spectrum, n is a positive real number, reducing the steepness defined by the original exponent (α becomes less negative). The resulting ratio is then a new, negatively sloped power law function. This coheres with the findings indicating the frequency-dependent levelling off of the excess sleep EEG spectral power in conditions of increased sleep pressure. In short, if we assume that sleep pressure is reflected by the spectral exponent of the sleep EEG, the detailed binwise spectral findings of previous reports can be modelled elegantly in a compact index characterizing the overall frequency composition of brain electrodynamics.

4.1.4. Variations on the spectral exponent theme

Different terms emphasize different, but tightly interrelated aspects of the power law-type spectra. Thus, the spectral exponent is frequently termed as a measure of the fractal component of the power spectrum (Wen and Liu, 2016) or as aperiodic activity (Gerster et al., 2022). The former term refers to the fairly stable dominance of lower over higher frequency bins in the spectra over a wide range of frequencies. In turn, aperiodic activity refers to the time series from which the spectra are derived from. The term aperiodic activity suggests that these time series are not made up by oscillations (periodic, rhythmic activity), but rather broadband, self-similar random processes with stable statistical properties over a wide range of temporal scales. Furthermore, 1/f activity or 1/f scaling of the spectra is a historically grounded term, which refers to a subset of phenomena in the power law scaling domain, at least in the context of neuroscience and or behavioural phenomena. The logic behind using the term 1/f-type scaling finds its roots in the fact that the spectral exponent is negative in the formula put forward above, whereas it becomes positive when transformed to $1/f\alpha$. That is $f\alpha = 1/f\text{-}\alpha$ or vice versa: $f\text{-}\alpha = 1/f\alpha$. Furthermore, the term 1/f suggests that the absolute value of the exponent roughly equals 1 ($0.5 < |\alpha| < 1.5$, implying pink noise). In cases, if an exponent is indicated (e.g. $1/f\alpha$ or 1/fx), the term is a synonym of power law scaling (Pereda et al., 1998; Pritchard, 1992). Last, the term scale-free activity means the lack of a predominant temporal scale of the time series (Table 2).

4.1.5. Specific spectral exponents define specific time series

Specific ranges of spectral exponents define specific signal characteristics of the underlying time series. A spectral exponent of $\alpha \approx 0$ indicates white noise. The term white refers to the colour of visible light with a spectral exponent equalling 0. This type of data implies a flat spectrum. In other words, power of white noise type processes is independent of frequency (Schroeder and Wiesenfeld, 1991). Time series with a white noise behaviour are known to be characterized by a complete independence of the successive samples (amplitude values). Given, the partial persistence of biological systems, to the best of our knowledge, no pure white noise type of EEG record was reported in the literature. Nevertheless, white noise, along with pink noise (see below) and spectral peaks was considered an integral part (component) of the EEG spectrum by some authors (Barry and Blasio, 2021).

Pink noise is defined by a spectral exponent of $\alpha \approx -1$, meaning a decrease in power along the frequency scale according to the proportionality formula of $P(f) \propto f^{-1}$ or $P(f) \propto 1/f$ (Fig. 2B). Time series with pink noise-type behaviour are made up by a succession of values, which unlike white noises, depend on each other. Indeed pink noise-like (also known as 1/f) time series were shown to continuously integrate the effects of their own recent and more distant past with the influence of random events (Keshner, 1982), as well as to provide an ideally suited platform for complex networks and may therefore be the channel through which the brain influences complex processes and is influenced by them (Allegrini et al., 2009). Another intriguing peculiarity of pink noise is its antipersistence: successive increments of the time series tend to correlate negatively. In fact, this is a feature of all time series with a spectral exponent of $\alpha > -2$ and is usually described by another index of statistical predictability, called the Hurst-exponent (H-exponent). Without entering into the details of estimating the H-exponent, we only draw the attention toward the convertibility of the spectral to the Hurst-exponent and vice versa, by using the following formula (Yamamoto and Hughson, 1993):

$$-\alpha = 2H + 1 \tag{5}$$

$$H = -\frac{1+\alpha}{2} \tag{6}$$

It turns out that pink noise is characterized by a H-exponent equalling $H = 0$. If $H < 0.5$, the time series can be considered as antipersistent (increases followed by decreases and vice versa).

Red noise, also known as Brownian noise is characterized by a spectral exponent of $\alpha \approx -2$. A power decrease along the frequency scale is faster than in the case of pink noise (i.e. the relative predominance of lower frequencies is higher, Fig. 2B). The autocorrelation function of red noise is high at low time lags, but drops off rapidly in time, indicating the relatively strong effect of the recent past on actual amplitude values, but a diminished influence of distant past (Keshner, 1982; c.f the term random walk). In turn, successive increments of red (Brownian) noise are completely independent which is reflected in the critical value of $H = 0.5$.

The term black noise is used for time series characterized by a spectral exponent of $\alpha \approx -3$. Drop off of spectral power of black noise along the frequency axis is even faster than in the case of red noise (c.f. lower frequencies predominate even more higher ones, Fig. 2B). Both amplitude values and successive increments tend to correlate positively in these types of signals. The latter means that black noise is persistent ($H > 0.5$).

EEG time series are often characterized by fractional spectral exponents, not just integers. This is highlighted in the term fractional Brownian motion, which can be divided into antipersistent ($H < 0.5$) and persistent ($H > 0.5$) types. While measurements using EEG power have yielded exponent values varying between -1 and -4 (Freeman and Zhai, 2009; He et al., 2010; Milstein et al., 2009; Zempel et al., 2012), some available evidence suggests that EEG or LFP recorded during wakefulness follow antipersistent dynamics, while those recorded during sleep tends to follow persistent dynamics (Lina et al., 2019; Schneider et al., 2022; B. Weiss et al., 2011).

Last, it has to be emphasized that human EEG is most frequently a combination of aperiodic and oscillatory activity, characterized by power law type spectra with Gaussian spectral peaks. The latter confer a high level of predictability of the signal in the frequency range of the peaks.

Table 2
Variations on the spectral exponent theme.

Term	Meaning	Reference
Power law scaling	The power spectra (density) of the time series follows a power law function with a specific spectral exponent	Miller et al. (2009); Miskovic et al. (2019)
Fractal component of the spectrum	Power law behaviour in the Fourier spectrum of the time series: low-to-high frequency ratios repeat over several magnitudes	Yamamoto and Hughson (1993); Wen and Liu (2016)
Aperiodic activity	Broadband, non-oscillatory activity	Rosenblum et al. (2022, 2023)
1/f activity or scaling	The power spectra (density) of the time series can be described by a $1/f\alpha$ function. (Original meaning: pink noise with an exponent equalling 1).	Lendner et al. (2020); Kozhemiako et al. (2022)
Scale-free activity	Lack of a predominant temporal scale of the time series	He (2014)

4.2. Indexing sleep homeostasis: looking at the spectral exponent of the EEG

4.2.1. The EEG spectral exponent reflects sleep-wake history and correlates with SWA

The earliest finding indicating the overall change in lower relative to higher frequency EEG activity as a function of time spent asleep is based on period amplitude analysis indicating a negative correlation between the logarithm of NREM sleep EEG amplitude and the logarithm of frequency in the 0.5–12 Hz range. The slope of this negative correlation was shown to decline in successive NREM periods, especially in young adults, and to a lesser extent in healthy aged subjects (Feinberg et al., 1984). More recent analyses of the overnight dynamics in scalp-recorded

NREM sleep EEG spectral exponents derived by relying on Fourier transformation revealed a progressive flattening of the slopes in successive sleep cycles (NREM periods, range: 2–48 Hz) (G. Horváth et al., 2022). Moreover, spectral exponents correlated negatively with SWA (31–53% of shared variance throughout the NREM periods), such that steeper decay was related to higher SWA energy, providing a convergent validity of the former measure (G. Horváth et al., 2022). It is important to note that delta (0.5–4 Hz) power correlated negatively with spectral exponent even during wakefulness in both eyes open and eyes closed conditions, whereas theta (4.5–7.5 Hz) power correlated negatively with slope in eyes open states only (Pritchard, 1992). The above studies suggest that the spectral exponent is a promising alternative marker of sleep-wake history, being characterized by convergent validity tested against the gold standard measure (SWA, Fig. 3A).

4.2.2. The EEG spectral exponent reflects arousal, vigilance, consciousness and sleep stages

Early reports and proof of concept studies revealed that wakefulness and sleep states can be reliably discriminated by the spectral exponents of the associated human EEG and electrocorticography records (Freeman and Zhai, 2009; Pereda et al., 1998; Zempel et al., 2012). Moreover, these findings indicate a clear association of steeper spectral slopes (more negative exponents) with sleep as compared to wakefulness. Accordingly, double logarithmic representations of the EEG power spectra in the 0.5–35 Hz range were increasingly more negatively sloped from the REM phase to stages N2 to N3 sleep (Miskovic et al., 2019). By focusing on the 2–48 Hz range, a gradual decrease of slope values (decreasing spectral exponents, increasing steepness) during the course of deepening of NREM sleep, as well as a relatively increased slope in REM sleep (but still below the AASM N1 stage values) were revealed (Schneider et al., 2022; Fig. 3B). Likewise, chemically-induced decreases in vigilance by reliance on the potentiation of gamma-aminobutyric acid (GABA)-A mediated inhibition during propofol anaesthesia were shown to decrease the spectral exponents of the EEG in the 1–40 Hz (Colombo et al., 2019) and 3–55 Hz (Waschke et al., 2021) ranges. Similar findings were reported for anaesthesia induced by xenon, a competitive antagonist of the N-methyl-D-aspartate (NMDA) receptors- in the 1–40 Hz range (Colombo et al., 2019). Higher frequency estimates relying a narrower focuses of 30–50 Hz in various EEG and electrocorticography recordings or 30–45 Hz in a particularly large sleep EEG dataset (N = 10 225) revealed similar conclusions: slopes were steeper in sleep or propofol anaesthesia as compared to wakefulness, but REM sleep was revealed to be even more negatively sloped than NREM sleep, including SWS, which is usually seen as the deepest sleep stage, by relying on these approaches (Kozhemiako et al., 2022; Lendner et al., 2020). In light of the above cited findings, it is not surprising that several attempts to automatically classify sleep records into stages relied in part on the spectral exponent measure (Demirel et al., 2021; Hassan et al., 2015) or heterogeneous random walks of the EEG (Metzner et al., 2021).

Our formerly published results indicate that the EEG spectral exponent of $\alpha = -2$ could be a critical value delimiting wakefulness and sleep states in the majority of subjects (Schneider et al., 2022). Likewise, broadband EEG spectral exponent values derived from awake, resting state-records reveal $\alpha > -2$ values in both healthy (Colombo et al., 2019; Muthukumaraswamy and Liley, 2018; Walter and Hinterberger, 2022) and clinical samples (Lanzone et al., 2022), but not in subjects anesthetized with propofol or xenon (Colombo et al., 2019). Although not explicitly emphasized, the latter states are characterized by EEG spectral exponents below the assumed critical value ($\alpha < -2$) (Colombo et al., 2019). This value is also known for a mathematically well-defined limit between antipersistent and persistent fractional Brownian motion, characterized by negatively and positively correlating successive increments of the time series, respectively. Similar findings in terms of the H-exponent of human EEG (B. Weiss et al., 2009, 2011) and the wavelet analysis-based spectral exponent of rodent EEG (Lina et al., 2019) were published. Authors of the latter paper ascertained that „…scale-free activity was more anti-persistent (i.e., more different between time scales) during wakefulness, less anti-persistent (i.e., less different between time scales) during non-rapid eye movement sleep, and generally intermediate during rapid eye movement sleep" (Lina et al., 2019). That is sleepiness as a subjective perception of sleep need, as well as the objective signs of advanced sleep pressure before initiating sleep per se, should be tested in terms of the spectral exponent of the EEG. Indirect evidence supporting the feasibility of this approach is promising. One set of reports supports the reliability of wakefulness-derived theta EEG activity in reflecting sleep homeostasis (Finelli et al., 2000; Snipes et al., 2022). Furthermore, resting state theta EEG power was reported to correlate with the spectral exponent (Pritchard, 1992). In addition, drug-induced sleepiness of human volunteers, namely light sedation following the administration of subanesthetic doses of the GABA reuptake inhibitor tiagabine or the glutamatergic AMPA receptor antagonist perampanel was associated with modest decreases in magnetoencephalography spectral slopes as compared to the placebo conditions, the α values remaining in the antipersistent range ($\alpha > -2$) (Muthukumaraswamy and Liley, 2018). In our view the decreasing resting state EEG spectral exponent values approaching the assumed critical level of $\alpha = -2$ are hypothesized to initiate appetitive behaviour, that is the feeling of sleepiness or even the search for the opportunity of initiating sleep, the latter being defined as the consummative behaviour. It remains to be determined if the EEG spectral exponent of $\alpha = -2$ can be considered as critical in awake subjects suffering from chronic sleep deprivation or repeated sleep restriction. Experimental works revealed clear evidence for detrimental neurocognitive effects of cumulative sleep loss due to consecutive restrictions of sleep time (Lowe et al., 2017). These effects are commonly paralleled by apparent adaptations in terms of subjective sleepiness and EEG theta power as measured during wakefulness (no dose-response relationship detected), leaving the issue of the neural underpinnings of cognitive deficits largely unresolved (Van Dongen et al., 2003). The low distance of the spectral exponents of EEG records derived from awake subjects from the assumed critical value of $\alpha = -2$ might constitute a candidate indicator of the detrimental neurocognitive effects of sleep debt, as empirical and theoretical evidence suggests that brain criticality is sensitive to extending the length of wakefulness (Meisel et al., 2013) and might be the primary target of the function of sleep, the latter being a tuning for criticality (Pearlmutter and Houghton, 2009, 2013; Xu et al., 2024).

The unequivocal evidence suggesting that arousal, vigilance and sleep stages differ in terms of the spectral exponents of the EEG is supported by further, albeit indirect findings. Recent human neurophysiology data indicate that the EEG spectral exponents derived from the 30–45 Hz range positively correlate with pupil size, a marker of arousal levels during human sleep, most likely reflecting activity of the locus coeruleus-noradrenergic system (Carro-Domínguez et al., 2023). Furthermore, evidence derived from animal studies unravelling the neuromodulatory bases of cortical local field potential (LFP) are suggestive in this regard. Reports support the role of acetylcholine and noradrenaline in enhancing arousal and improving sensory processing or attention (E. Weiss et al., 2023). In addition, the extracellular levels of these neuromodulators are known for their significant change throughout the wakefulness-sleep cycle (B. E. Jones, 2005). Parallel findings revealed that the stimulation of the cholinergic nucleus basalis region in rats acutely increased higher to lower frequency cortical LFP power ratio (LFP power at 10–100 Hz divided by that at 1–10 Hz) (Goard and Dan, 2009). Similar findings were reported by the experimental stimulation of the locus coeruleus, the main noradrenaline source in the brain: an immediate shift toward higher frequencies (increased high to low frequency power ratio), but apparently maintained linear power decay in the double logarithmic plain were evident (Liu et al., 2017). Given the widespread correspondence and convergence of spectral exponent-related and band-limited power ratio-derived findings in the electrophysiological studies of vigilance (Donoghue et al., 2020), as well as the fact that the spectral exponent is

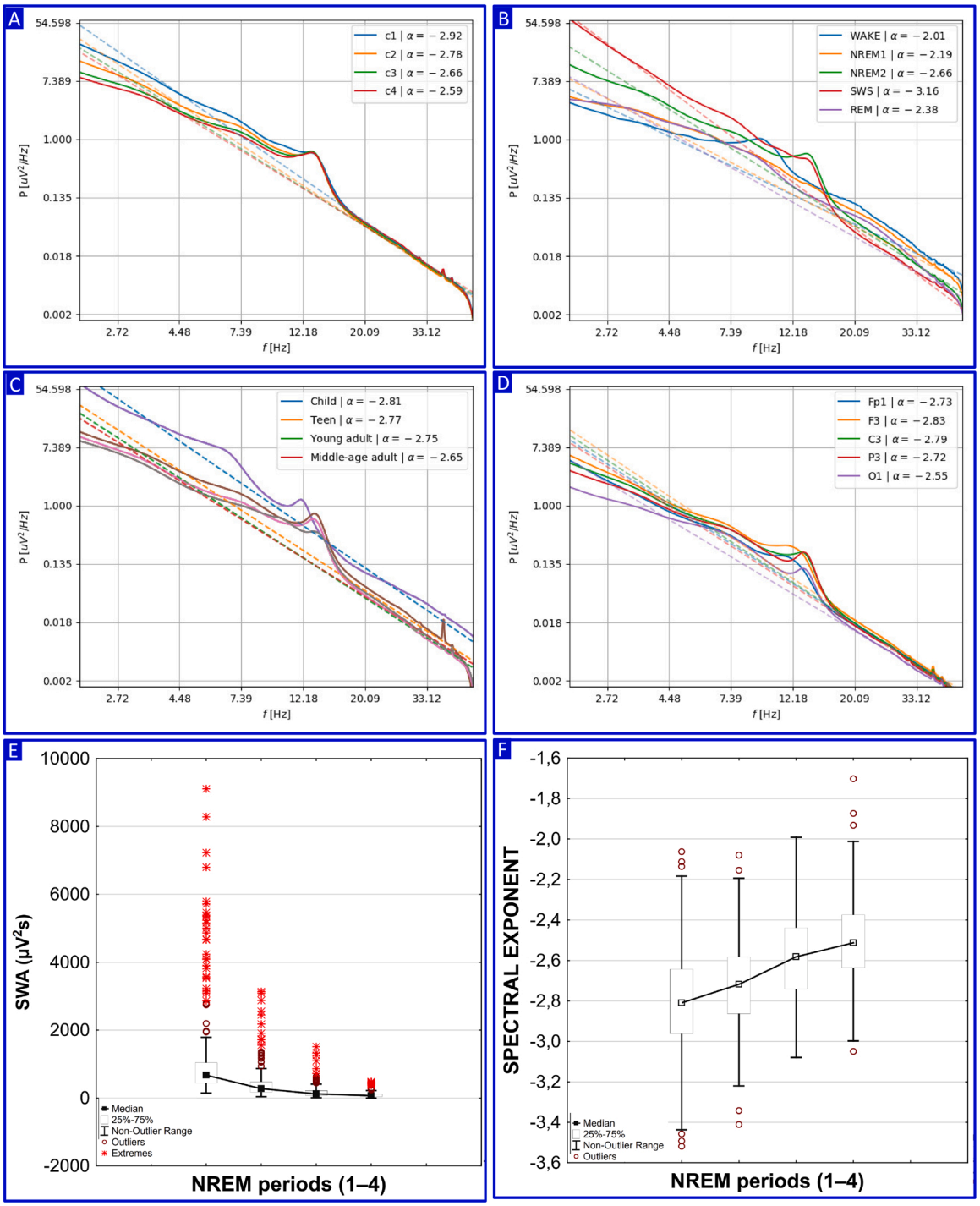


Fig. 3. The spectral exponent as a composite measure of sleep-wake-EEG and sleep pressure in humans. A. The NREM sleep EEG spectral exponents reflect increased levels of sleep pressure related to sleep-wake history: spectral slopes in consecutive cycles of sleep (c1–c4). B. The EEG spectral exponents reflect increased levels of sleep pressure related to AASM sleep stages. C. The NREM sleep EEG spectral exponents reflect increased levels of sleep pressure related to development and aging: spectral slopes in different age groups. D. The NREM sleep EEG spectral exponents reflect increased levels of sleep pressure related to brain topography: front-back differences in spectral slopes. E. Medians, interquartile ranges, outliers, and extreme values in NREM sleep periods 1–4 EEG SWA (left prefrontal recording location F3, referred to the mathematically-linked mastoids). Note the high interindividual variation hindering the possibility to define reference values. F. Medians, interquartile ranges, and outliers in NREM sleep periods 1–4 EEG spectral exponents (left prefrontal recording location F3, referred to the mathematically-linked mastoids). Note the low interindividual variation providing us with the possibility to define reference values. Data presented in this figure is derived from two published reports, both based on second night sleep records of N = 251 healthy subjects (age range: 4–69 years, 122 females) from the Budapest-Munich database. Power spectral density data were derived from mixed-radix FFT analyses of non-artefactual, 4 s Hanning tapered windows with 50% overlap (G. Horváth et al., 2022; Schneider et al., 2022).

an implicit measure of power ratio, the above results are indicative of decreasingly negative spectral exponents (decreases in log-log slope steepness) in states of vigilance and high arousal. Moreover, findings suggest that acetylcholine and noradrenaline are involved in higher spectral exponents (flatter slopes) in conditions of high arousal and vigilance.

Indeed, decreasing vigilance and inducing somnolence and general anaesthesia by means of various pharmacological agents consistently decreased the spectral exponent of the EEG in human subjects, increasing the steepness of their spectral slope in the double logarithmic plain. Moreover, the spectral exponent was effective in indexing the presence of conscious awareness in these states (Colombo et al., 2019). An intriguing finding indicates the potential role of spectral exponents in tracking the subtle peculiarities in conscious awareness during sleep. Thus, patients suffering from sleep state misperception (experiencing wakefulness during periods of sleep as defined on the basis of standard scoring rules detailed in Table 1) were shown to be characterized by flatter N2 and N3 EEG spectra, meaning higher (less negative) exponents as compared to (objectively and subjectively) good sleeper controls (Andrillon et al., 2020). Flatter N2 and N3 spectra could indicate unusually high levels of excitation during sleep, which coheres with the hyperarousal model of insomnia.

4.2.3. The EEG spectral exponent reflects development and aging

As indicated above, the logarithm of NREM sleep EEG amplitude was found to be a linear function of the logarithm of frequency (0.5–12 Hz) in both healthy young and elderly subjects, as revealed by period amplitude analysis. In addition, the steepness of the slope describing the negative correlation between the logarithm of EEG amplitude and the logarithm of EEG frequency was significantly lower in older as compared to younger subjects (Feinberg et al., 1984). Later studies based on the Fourier analysis approach and extending the frequency range to 0.3–45 Hz largely confirmed this age-related difference (Tan et al., 2001). Furthermore, age was consistently shown to be a predictor of the EEG spectral exponents in both wakefulness (Voytek et al., 2015) and sleep including NREM and REM phases (Bódizs et al., 2021; Kozhemiako et al., 2022), all NREM periods (G. Horváth et al., 2022) and AASM stages (Lendner et al., 2020; Schneider et al., 2022).

Besides the formerly presented supporting evidence, the appropriateness of the spectral exponent in depicting sleep homeostasis is further strengthened by the overnight dynamics of this measure in different age groups. Whereas SWA and log-normalized SWA are persistently different among prepubertal and postpubertal ages during the course of night sleep, this age-effect vanishes during the night in terms of the spectral exponent. That is, steeper NREM sleep EEG spectra during early sleep in children as compared to adults are equalized during the course of night sleep (G. Horváth et al., 2022). This coheres with recent findings reporting no significant differences in all-night means of NREM sleep EEG spectral exponents between children and adolescents (Favaro et al., 2023). If we assume that homeostasis implies feedback processes promoting the maintenance of or return to a steady state, the disappearance of the initially large age-differences during the course of the night could be considered as a conceptually valid approximation of this regulation in the sleep domain.

Additional empirical evidence for the age-dependent flattening of sleep EEG spectral slopes can be derived from the frequency distributions of aggregated exponent values (α) acquired by instantaneous parametrizations of all-night polysomnography records (Fig. 4.A). It seems that exponent values corresponding to black noise decrease in successive age groups, whereas a secondary peak of pink noise emerges in young adults/middle aged subjects, indicating the age-dependent decrease in sleep pressure and/or increase in shallow sleep/wakefulness, respectively. In addition, these distributions are suggestive for the robustness of the spectral exponent-based approach in quantifying sleep intensity, as the results presented in Fig. 4.A are obtained from non-selected records, containing all sleep stages and artefacts.

4.2.4. The EEG spectral exponent as a function of localization

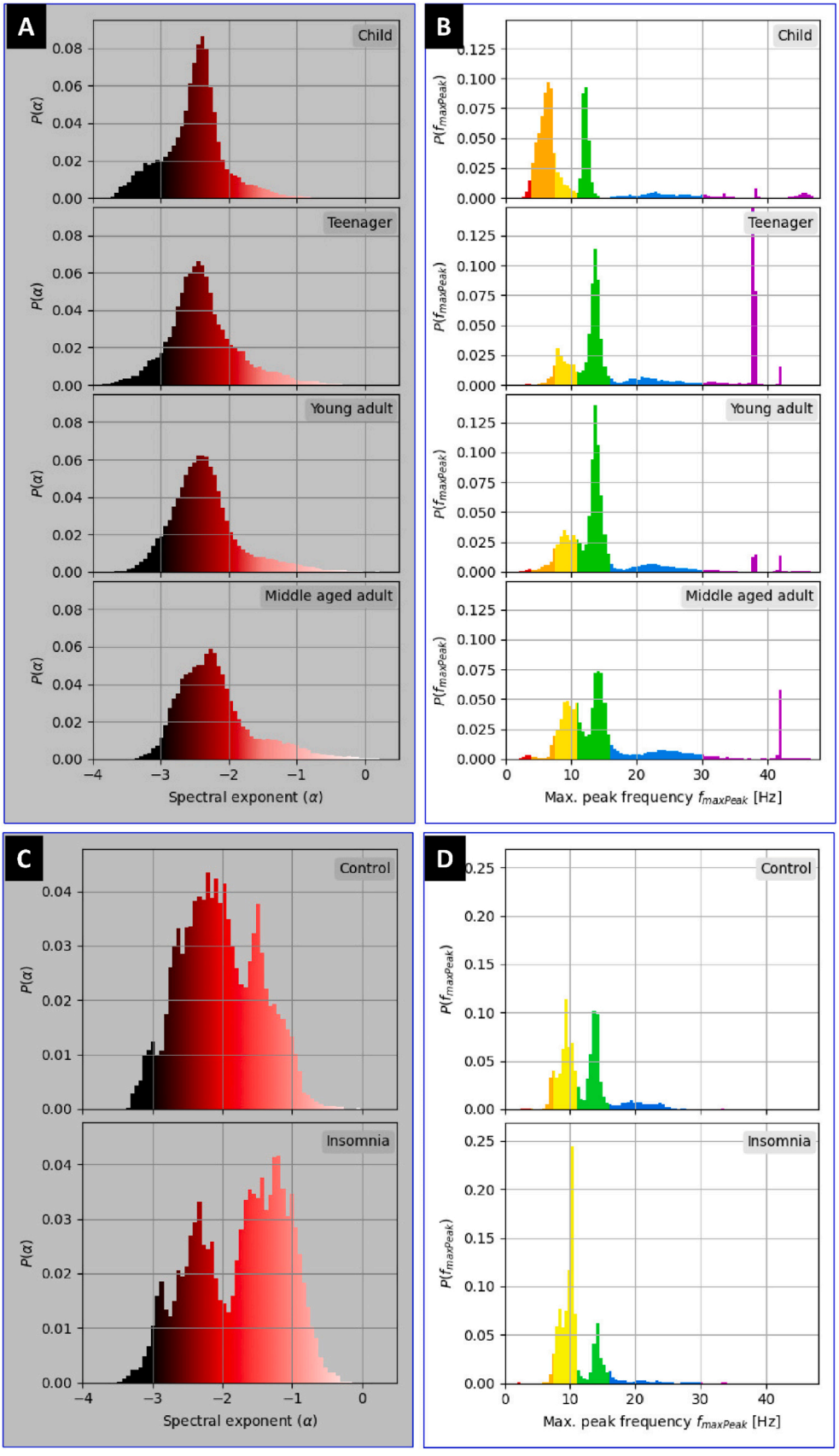
Topographical effects in EEG spectral exponents were revealed in several studies comparing the power vs frequency relationship at different recording locations. Midline frontal, central and parietal recording sites were characterized by the highest spectral steepness during wakeful resting conditions in the pioneering study of (Pritchard, 1992), whereas significant antero-posterior gradients in spectral exponents were reported by several studies focusing on sleep EEG. Anterior recording sites resulted in more negatively sloped spectra as compared to posterior ones in individual NREM sleep periods (G. Horváth et al., 2022). The anteriority effect in spectral exponent was maximal during N3/SWS (Schneider et al., 2022), whereas the location with steepest spectra undergoes a shift from posterior to anterior regions from childhood to adolescence, particularly during sleep (Favaro et al., 2023). Given the fact that frontal EEG spectral slopes were consistently found to be steeper in NREM sleep, especially in the deepest stages of sleep known for their involvement in sleep homeostasis, these findings cohere with the topography of sleep intensity and the prevailing frontal predominance of SWA (Fig. 3D).

4.3. The EEG spectral exponent as a reference value

As discussed above the lack of appropriate, empirically well-founded and widely accepted reference values can be considered as an Achilles' heel of all known indexes of sleep homeostasis. Particularly large interindividual differences interfere with attempts to define benchmarks or references in the time spent in SWS (S3 and S4, or N3 amounts) or SWA, whereas the relativization or log-normalization of the spectra might bring in its train new problems. Due to its scale-free properties the spectral exponent α is an ideal candidate for deriving reference values. Although age-effects in sleep intensity are reliably reproduced by the NREM sleep EEG spectral exponent (Bódizs et al., 2021), as well as by its historical forerunner, the slope of the negative correlation between the logarithm of amplitude and the logarithm of frequency (Feinberg et al., 1984), the range of interindividual differences does not seem to override the sleep regulatory effects. In other words, interindividual differences are depicted, but not exaggerated by the spectral exponent, which we assumed to be the case for SWA or delta EEG power. In an explicit attempt to compare the interindividual variability in spectral exponents with a respective measure of both raw and log-normalized SWA, we considered the number of outliers and calculated the coefficient of variation (relative standard deviation) for these measures in the NREM sleep EEG of healthy volunteers' all-night polysomnography records. Results indicate a considerably lower number of outliers in the spectral exponent measure, as compared to the absolute and log-normalized SWA. Accordingly, the coefficients of variation were 2–3 times lower for the spectral exponent as compared to the respective values derived for SWA indices. That is, the spectral slope is a less individual-specific metric (G. Horváth et al., 2022). Benchmark values for the EEG spectral exponents in various age groups are indicated in Table 3. Data on this normally distributed metric are derived from the baseline, post-adaptation nights from various studies conducted on subjects of 4–69 years of age (G. Horváth et al., 2022; Schneider et al., 2022) and might be considered as starting points of a clinically approved and useful set of reference values. In order to promote methodological pluralism, which we think is inevitable at this stage of knowledge in the field, benchmark data obtained by an alternative method is provided in Supplementary table 1.

4.4. The EEG spectral exponent reflects alternating up and down states (bistability)

Several independent series of investigations aimed to unravel the neural bases of the ubiquitous Brownian types of power laws, frequently seen in mammalian LFP power spectra. Although these investigations did not explicitly focus on the sleep-wake state-dependency of power



(caption on next page)

Fig. 4. Redistribution of aperiodic and oscillatory EEG frequencies in successive age groups and clinical conditions reveals the robustness of spectral parametrization against sleep staging and noise. A. Relative redistribution of probabilities (P) of obtaining black noise-type EEG segments toward hazards of seeing pink noise-type epochs from childhood to middle aged subjects coheres with the reported age-related changes in sleep composition (α – spectral exponent). B. Redistribution of probabilities of obtaining theta (4–7 Hz) maximal peak frequencies ($f_{maxPeak}$) in the whitened spectra of children toward alpha (7–11 Hz) and beta (16–30 Hz) spectral peaks in middle aged subjects. Findings cohere with the reported increases in oscillatory alpha and beta frequencies in the aged reflecting shallow or more activated sleep states/wake after sleep onset. C. Redistribution of probabilities (P) of obtaining black noise-type EEG segments toward hazards of seeing pink noise-type epochs in psychophysiological insomnia as compared to control subjects coheres with the reported flattening of EEG spectra in insomnia (α – spectral exponent). D. Redistribution of probabilities of obtaining spindle (11–16 Hz) maximal peak frequencies ($f_{maxPeak}$) in the whitened spectra of control subjects toward alpha (7–11 Hz) spectral peaks in insomnia subjects. Findings cohere with the reports on alpha activity indexing arousal. Data depicted in panels A and B are derived from the Budapest-Munich database (N = 251 healthy subjects, age range: 4–69 years, 122 females) by the parametrization of all night sleep-wake EEG spectra according to the modified FOOOF procedure (Schneider et al., 2022) on moving averages of 75 consecutive periodograms of 4 s long, Hanning-tapered EEG-segments (overlap 74×4 s, left central recording location C3-A1A2, no sleep stage- and artefact-related information used, panels. Panels C and D depict data derived from an open database of N = 11 psychophysiological insomnia and N = 11 control subjects aged between 18 and 63 years (43.2±14.2), 14 females (Rezaei et al., 2017). Due to low-pass filtered EEG data used in panels C and D, the fitting of spectral slopes and peaks in these latter cases were performed in the 2–30 Hz range.

Table 3
Benchmark values for sleep EEG spectral exponents derived from the left central recording location (C3) of healthy subjects of different ages*.

	Group [age]	Children [4, 10[			Teenagers [10, 20[			Young adults [20, 40[			Middle-aged adults [40, 70[		
		Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
NREM	night average	-2.81	0.15	31	-2.73	0.21	36	-2.72	0.17	150	-2.63	0.14	34
	cycle 1	-3.17	0.18	31	-2.95	0.29	36	-2.89	0.22	150	-2.74	0.15	34
	cycle 2	-2.83	0.27	31	-2.76	0.23	36	-2.78	0.20	150	-2.72	0.19	34
	cycle 3	-2.60	0.24	31	-2.67	0.23	36	-2.67	0.20	148	-2.57	0.17	34
	cycle 4	-2.56	0.24	30	-2.58	0.23	36	-2.61	0.18	143	-2.51	0.18	30
REM	night average	-2.49	0.17	31	-2.39	0.22	36	-2.36	0.14	150	-2.27	0.13	34
	cycle 1	-2.70	0.16	29	-2.50	0.20	30	-2.44	0.17	139	-2.31	0.16	33
	cycle 2	-2.57	0.21	31	-2.44	0.23	36	-2.38	0.17	148	-2.32	0.15	34
	cycle 3	-2.52	0.14	31	-2.40	0.22	36	-2.36	0.17	146	-2.27	0.15	34
	cycle 4	-2.46	0.21	30	-2.37	0.23	35	-2.35	0.18	143	-2.23	0.15	29

* Data obtained by using the FOOOF procedure (Donoghue et al., 2020) on the Budapest-Munich database (Bódizs et al., 2017); EEG reference: mathematically-linked mastoids; night average refers to the average spectra of all night NREM or REM sleep, including all available sleep cycles

spectra, a common solution of the endeavours find its roots in the up-down state alternation, which is an inherent property of low vigilance, NREM sleep and general anaesthesia. According to one modelling study completed by human LFP recordings derived from invasive epilepsy monitoring settings, the random alternation of periods of sustained, rapid cortical activity followed by intervals of inactivity (telegraphy process) gives rise to a Brownian-type power spectrum, characterized by a spectral exponent of $\alpha = -2$ in the frequency range of 1–400 Hz (Milstein et al., 2009). That is, bistability in itself could cause power spectra which are scaled like the ones derived from random motion of particles suspended in a medium. Furthermore, Brownian type of power law scaling ($\alpha = -2$) in the LFP power spectrum was found to be largely generated by the step like transitions between cortical up-down states in rats. Moreover, these transitions were hypothesized to be induced by synchronous changes in the membrane potential across neurons (Baranauskas et al., 2012). It is worth noting that these studies did not specifically investigated sleep, thus the fact that their authors invoke up-down state alternation seems largely non-appropriate at first sight. However, sleep was not excluded from the records in neither of the studies, thus it could contribute to the spectra by up-down state alternation. Moreover, if we consider the emergence of local down states in the LFP of behaving rats (Vyazovskiy et al., 2011) and humans (Slater et al., 2017), the explanations could partially fit within the framework of sleep-wake state regulation. In spite of the suggestive contribution of burst-like thalamocortical activity contributing to the findings, the above theoretical models were not confirmed in the light of the behavioural state-dependent changes of up-down state characteristics and spectral slopes. In addition, explanations are constructed on the level of system neuroscientific approaches, which might be appropriate, but leaves space for cellular level groundings of the spectral exponents.

4.5. The EEG spectral exponent as a measure of excitation/inhibition (E:I) ratio

A potential source of power law type spectra is a time series derived from the superposition of a range of relaxation processes, similarly to the varying recovery times of neurons after firing (Schroeder and Wiesenfeld, 1991). Uncorrelated cells that display sharp initial activity, whose extracellular fields slowly decay in time were hypothesized to give rise to a Brownian type of LFP power spectra (Milstein et al., 2009). A further elaboration of this approach postulates that the difference in the time constants of the decays in post-spiking extracellular fields of excitatory and inhibitory neurons determine the steepness of the spectral slope of the LFP spectra. Steeper slopes indicate a higher involvement of inhibition, as inhibitory neurons normalize their post-spiking membrane potential at a slower rate (membrane potential changes are more persistent). As a consequence, excitation-to-inhibition (E:I) ratio can be inferred from the value of the spectral exponent or the steepness of the slope in double logarithmic coordinates (Gao et al., 2017). An important point in this model is the issue of the critical frequency range in spectral slope steepness which was found to vary according to the value of the E:I ratio itself. Modelling indicated that E:I ratio is positively correlated with PSD slope between 30 and 50 Hz in many instances. It has to be noted that up-down state alternation and E:I ratio are not exclusive explanations of neural power law type spectra. As down states are characterized by widespread hyperpolarization and were originally termed as hyperpolarization states by Mircea Steriade and his collaborators (Steriade et al., 1993), the inherent association of the two phenomena is evident.

Further, indirect evidence supporting the relationship between neural excitation and the spectral exponent comes from the already mentioned studies focusing on neuromodulation and low over high frequency LFP. Noradrenaline exerts primarily excitatory postsynaptic effects in cortical neurons by stimulating α1 and β receptors (Holland et al., 2021; Johnson et al., 1968; Koga et al., 2020), whereas the

stimulation of the locus coeruleus, the main source of central nervous system noradrenaline resulted in immediate shift to the relative increase in high (10–100 Hz) over low (1–10 Hz) frequency LFP power, but roughly maintained power law type scaling (Liu et al., 2017). Likewise, acetylcholine release in the cortex can induce activation of pyramidal neurons by two parallel mechanisms related to muscarinic and nicotinic receptors (Carcea and Froemke, 2013), whereas the experimental facilitation of this release results in increased high over low frequency LFP (Goard and Dan, 2009).

In sum, the spectral exponent of the EEG is not just an expression of the constant ratio of lower/higher frequency power, but also a composite and non-redundant mathematical abstraction formalizing several regularities of sleep homeostasis. The latter encompass the law of diminishing return, reflection of sleep-wake history, sleep stage differences, development and aging, as well as brain topography and local differences in sleep intensity. In addition, the spectral exponent is suitable for building reference values, because of its lower interindividual variability as compared to SWA and due to the existence of specific exponent values determining specific time series dynamics. Last, but not least, the EEG spectral exponent is related to neurophysiological processes formerly revealed to be critically involved in sleep regulation, including network bistability, E:I ratio and the release of key neurotransmitters, like noradrenaline, acetylcholine, GABA, and glutamate.

5. Basic sleep regulatory processes: circadian rhythmicity

5.1. Basic concepts of circadian rhythmicity and their applicability to sleep

A significant growth in understanding the maintenance of the stability of the internal milieu of the organism emerged after the recognition of the anticipatory types of adaptive mechanisms working in strong association with the biological clocks, especially the master circadian timer (Moore-Ede, 1986). This type of predictive homeostatic mechanism was hypothesized to play central role in the regulation and function of sleep (Simor et al., 2023). In other words, the circadian rhythms or Process C can be considered as a timer of sleep and wakefulness, with prevailing night-time sleep promotion in diurnal beings, including humans (Borbély, 1982; Borbély et al., 2016). The anatomo-functional basis of the self-sustaining circadian oscillator is found within the master circadian pacemaker, known to be located in the suprachiasmatic nuclei of the hypothalamus. Neurons of the suprachiasmatic nuclei tend to fire at a higher rate during the day and lower their activity during the night. Clock genes (Period and Cryptochrome) within the neurons of the suprachiasmatic nuclei express clock proteins during the biological day, whereas clock proteins form dimers and translocate to the cytoblast, inhibiting their own further expression. The inhibition of clock gene expression by clock protein dimers in the cytoblast is attained by repressing the CLOCK-BMAL1 transcription factors, the latter effect prevailing during the biological night. This transcriptional-translational feedback loops repeatedly with an approximate cycle length of 24 hours and relatively high persistence (Maywood, 2020; Young, 2018), at least compared to the flexibility of sleep homeostasis. External timers, called Zeitgebers provide an appropriate adjustment of circadian phase to external physical or social requirements. Suprachiasmatic nuclei neuronal activity is a timer of regular night-time pineal melatonin release. Given the preponderance of melatonin receptors in the suprachiasmatic region, melatonin feeds back on the master circadian clock, strengthening the “night-mode” of activity, whereas light has an opposite effect. Light is known to induce an acute activation of suprachiasmatic nuclei neurons via the retinohypothalamic tract, an effect associated with immediate early gene and Period2 gene expression in these cells. Moreover, pineal melatonin is acutely supressed by light. These effects convey a “day-mode” message to the master clock (Borjigin et al., 2012; Pevet and Challet, 2011).

5.2. Indexing circadian rhythms: classic measures and some EEG correlates

Markers of circadian rhythm include behavioural indices like questionnaires, sleep logs/diaries, and rest-activity rhythms as measured by actigraphy. Furthermore, biometric markers include drops in core body temperature and release of melatonin during the biological night, as well as clock gene expression assessed in whole-blood samples, peripheral blood mononuclear cells, oral mucosa or hair and beard follicles (Crnko et al., 2021; Reid, 2019). Recently proposed, new measures indicating circadian rhythms include one or a few samples of high dimensional data derived from transcriptomes and/or metabolomes (Dijk and Duffy, 2020). The gold standard method of circadian phase assessment is the so called Dim Light Melatonin Onset procedure involving the detection of the individual starting times of melatonin production by analysing saliva samples in conditions of low ambient illumination during evening hours (Lewy and Sack, 1989; Pandi-Perumal et al., 2007).

According to the widely acknowledged claim, polysomnography is not useful in the diagnosis or treatment of circadian rhythm sleep disorders (Chokroverty et al., 2005). This could be one of the reasons of the fact that the time-course of Process C in the two-process model of sleep regulation was derived from physiological and behavioural variables, but not from EEG measures (Borbély et al., 2016). Indeed, several EEG and polysomnographic measures of circadian phase were revealed. Most of these measures were not clinically validated yet, or were not specific enough to be translated to chronomedical settings. Examples of process - related polysomnography measures include alpha EEG activity (8.25–10.25 Hz) during REM sleep or REM sleep percent (relative to total sleep time) (Dijk et al., 1997), as well as the somewhat unexpected finding, indicating that the incidence, amplitude, frequency, and the slope of slow waves (0.5–4 Hz) were revealed to follow a circadian rhythm, with acrophases during the biological day and with prevailing centro-posterior topography (Lazar et al., 2015). In addition to these examples of polysomnogaphy-derived correlates of circadian regulatory processes, the oscillatory frequency of sleep spindles was also emphasized in some studies.

5.3. Indexing circadian rhythmicity: looking beyond the classical measures

5.3.1. Oscillatory sleep spindle frequency as a putative index of circadian phase

Sleep spindles are burst-like sequences of 11–16 Hz (most commonly 12–14 Hz) sinusoidal cycles in the EEG of N2 and N3 sleep stages with a duration $\geq$0.5 s according to the commonly used criteria (Fernandez and Lüthi, 2020; Kane et al., 2017). A minimum length of 0.5 s was not part of the original description of the phenomena, but the typical frequency of 14 Hz was already emphasized (Loomis et al., 1935). Spindle bursts constitute a common physiological oscillatory activity pattern in the human NREM sleep EEG, forming clear spectral peaks in the periodograms (Jobert et al., 1992). Frequency and antero-posterior topographical axis delineate slow (~12 Hz) frontally dominant and fast (~14 Hz) parietally dominant sleep spindles (Gibbs and Gibbs, 1951), usually forming two distinct spectral peaks in some but not all subjects (Gennaro et al., 2005; Jobert et al., 1992).

Studies conducted by the use of the forced desynchrony protocol (experimentally scheduled sleep on a 28 hours day basis) are instrumental in the differentiation of the effects of sleep-wake history and circadian phase on the specific EEG markers. Studies of this type revealed a predominant effect of time-of-day or circadian phase on the spectral power of NREM sleep EEG spindle frequency activity (Dijk et al., 1997) or more specifically on the oscillatory frequency of R&K Stage 2 sleep spindles. Spindle frequency reached its nadir at the trough of the body temperature cycle (Wei et al., 1999). In addition, spindle frequency showed a U-shaped overnight time course, significantly decreasing from a highest level in NREM episode 1 to NREM episode 2 and increasing

from NREM episode 3–4 (Bódizs et al., 2022; Knoblauch et al., 2003). The slowing of sleep spindle oscillations around 3–4 AM was revealed in a time-of-day-dependent analysis, after removing the effects of time elapsed since sleep onset (Purcell et al., 2017).

Further spectral analyses revealed similar findings in both forced desynchrony (Dijk, 1999) and sleep displacement (Aeschbach et al., 1997) studies. Specifically, spindle frequency activity as measured by a binwise approach, redistribute toward lower frequencies during the habitual night sleep period, whereas the opposite change was observed during transitioning toward the day. Furthermore, evenly spaced naps during the 24 hours day indicate that sleep spindle frequency decelerates during the night, when melatonin production peaks (Knoblauch et al., 2005), whereas daytime sleep following a night of total sleep deprivation is characterized by higher frequency sleep spindles, as compared to the baseline, nocturnal sleep period (Rosinvil et al., 2015). Last, but not least daytime nap sleep spindles were revealed to be faster than night sleep spindles (Bódizs et al., 2022), whereas the timing of the nadir in sleep spindle frequency reliably correlates with actigraphy-derived measures of circadian phase (G. Horváth and Bódizs, 2024).

Above reported evidence suggests that oscillatory sleep spindle frequency is a putative sleep EEG-based biomarker of circadian rhythms, with lower and higher values indicating biological night and day, respectively. The formalization of this assumption can be elegantly performed on the basis of the power law and spectral-peak scaling formula of the EEG presented in our previously published work (Bódizs et al., 2021) and in the current paper as well. The marker of process C could indeed be the location of the local maximum of the PPeak(f) function within the spindle range (fmaxPeak). In order to avoid shifts among slow-anterior and fast-posterior sleep spindle types, frequency ranges or recording locations have to be selected carefully. Alternatively, the parallel analysis of both slow and fast sleep spindles as embedded in the Individual Adjustment Method (IAM) of sleep spindle analysis (Bódizs et al., 2009) can be adopted.

5.3.2. *Sleep spindle frequency as a putative index of development and aging*

Age is a crucial variable in circadian biology. On the phenotypic level children are characterized by an advanced phase of their circadian rhythms as compared to adults. Data derived from the reported timing of sleep on free days indicate that phases age-dependently delay until the end of adolescence (roughly 2.5 hours delay until the age of 20 years), whereas adulthood is characterized by an age-dependent, slow, gradual phase advancement of circa 30 minutes/decade (Roenneberg et al., 2004). These findings are consistent with data on preferred schedules of sleep (Randler et al., 2016). Besides phase advancement, aging is also associated with the reduction of the amplitude of circadian modulation of several variables, including among others rest-activity rhythms, sleep, melatonin and cortisol release, as well as metabolic rate (Hood and Amir, 2017).

The above mentioned age-related alterations in circadian phase and amplitude are paralleled by similar changes in sleep spindle frequency. Thus, the estimated phases of the nadirs in sleep-spindle frequencies were advanced in children of 4–9 years as compared to teenagers (10–19 years), as well as young (20–39 years) and middle-aged (40–69 years) subjects by 1–2.5 hours, depending on spindle type (slow vs fast), age group and sex (Bódizs et al., 2022). Moreover, a notably lower amplitude of the circadian rhythm of R&K Stage 2 sleep spindles in older (64–72 years) as compared to younger (21–25 years) subjects was revealed in a forced desynchrony study (Wei et al., 1999). Accordingly, the deceleration of sleep spindle oscillations during the middle of the night-time sleep period attenuates in an age-dependent manner (Bódizs et al., 2022; Purcell et al., 2017). Night sleep spindle spectral peak frequencies of the whitened frontopolar EEG spectra (with a removed power law trend) confirmed this assertion: the lack of an U-shaped overnight dynamics is evident in middle aged subjects (40–69 years), whereas it is present in all other age groups (G. Horváth et al., 2022). Likewise, the significant day-night difference in nap sleep spindle frequency of younger subjects (20–31 years) was not revealed in older (57–74 years) volunteers (Knoblauch et al., 2005). Similar findings were reported for sleep periods of habitual length: daytime recovery vs night-time baseline sleep spindle frequency differed less in middle aged (40–60 years) than in young (20–38 years) subjects (Rosinvil et al., 2015).

In sum, available evidence suggests that oscillatory sleep spindle frequency measures are instrumental in depicting the age-related changes in circadian rhythmicity, including advanced phase in children and decreased amplitude or attenuated diurnal changes in middle-aged or older adults.

5.3.3. *Oscillatory sleep spindle frequency reflects core body temperature*

Temperature-dependence of EEG power spectral measures is widely reported in hibernating species, but could have potential relevance in humans as well. Accordingly, most biological processes have a temperature coefficient (Q10) between 2 and 3, such that the speed of the process doubles or triples as temperature increases by 10°C (Deboer, 1998). Although, this would mean just a few tenths of Hz changes in case of a sleep EEG oscillation throughout the physiological variations in body temperatures, these small fluctuations could provide us with cues regarding circadian phase.

In subjects with conventional sleep timing the nadir of core body temperature typically occurs during the latter part of the habitual sleep period (around 3–4 AM) (Reid, 2019). Moreover, forced desynchrony investigations revealed the coincidence in the nadirs of core body temperature and sleep spindle frequency rhythms in humans (Wei et al., 1999). In addition, unequivocal findings indicate an age-dependent attenuation in the amplitudes of both core body temperature (Hood and Amir, 2017) and sleep spindle frequency changes throughout the day (Bódizs et al., 2022; Wei et al., 1999).

Further correlative evidence suggesting the close correspondence between body temperature and sleep spindle frequency comes from the studies focusing on menstrual cycle-related variations in neural oscillations in females. Increased progesterone level during the luteal phase of the menstrual cycle is characterized by both increased core body temperatures (Baker et al., 2001) and accelerated sleep spindles (Driver et al., 1996; Ishizuka et al., 1994). The overall faster sleep spindles in females as compared to males was revealed in a wide reproductive age range (Bocskai et al., 2023; Bódizs et al., 2022; Markovic et al., 2020; Ujma et al., 2014) and could reflect the accelerated thalamocortical oscillatory dynamics in slightly hyperthermic luteal phase records of the menstrual cycles of women involved in the studies.

These indirect findings suggest a close correspondence between body temperature and sleep spindle frequency. Indeed, rodent models focusing on the effect of local brain temperature manipulations on neural oscillations revealed a positive correlation between temperature and sleep spindle frequency. The acceleration of sleep spindle by local warming followed a Q10 value perfectly fitting the biological range of 2–3 (Csernai et al., 2019).

5.3.4. *Oscillatory sleep spindle frequency reflects melatonin-release*

The reticular thalamic nucleus is a key neuroanatomical structure in the generation of sleep spindles, specifically involved in the hyperpolarization of thalamocortical neurons during periods of NREM sleep (Steriade, 2003). Melatonin receptors are expressed in the reticular thalamic nucleus (Ng et al., 2017). Besides the anatomical overlap mentioned above, diurnal/circadian, as well as age-related changes in melatonin and sleep spindle frequency are known to follow parallel patterns. As regarding the former, the acrophase of salivary melatonin level was shown to coincide with the nadir in sleep spindle frequency in humans (Knoblauch et al., 2005). Age-effects in melatonin production and sleep spindle frequency are also coherent with the hypothesis of their negative correlation. Nocturnal serum melatonin levels are around two times higher in prepubertal children as compared to adults

(Waldhauser et al., 1988), while this is an age range known to be characterized by particularly low sleep spindle frequencies (Ujma et al., 2014; Z. Y. Zhang et al., 2021). Furthermore, aging is associated with a slow reduction in melatonin release (Hood and Amir, 2017; Waldhauser et al., 1988; Wetterberg et al., 1999), as well as with an attenuation in circadian and/or overnight changes in sleep spindle frequency (Bódizs et al., 2022; Wei et al., 1999). Taken together these results might indicate the potential involvement of melatonin in the deceleration of sleep spindles during the biological night. However, the specific mechanism of this potential involvement is still largely unrevealed. One possibility is the indirect route, that is a sleep spindle deceleration effect of melatonin through hypothermia (Marrin et al., 2013), but direct neural mechanisms involving the core structure of sleep spindle generation cannot be ruled out.

6. Basic sleep regulatory processes: ultradian rhythmicity

6.1. Basic concepts of ultradian rhythmicity and their applicability to sleep

Ultradian rhythms or episodic ultradian events are rhythmic or episodic phenomena with a cycle length/recurrence rate of less than 24 hours, but usually between the limits of 20 minutes to 6 hours. These phenomena are ubiquitous in all biological systems, being rooted in many divergent molecular and brain mechanisms (Goh et al., 2019). Sleep is known to be organized in ultradian cycles made up by an alternation of NREM and REM phases in roughly 90 minutes long bouts (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957). Evidence suggests the pivotal role of the reciprocal interaction of REM-sleep inhibiting monoaminergic (serotoninergic dorsal raphe and noradrenergic locus coeruleus, termed REM-off) and REM sleep-promoting cholinergic (laterodorsal tegmental and peduculopontine tegmental, REM-on) nuclei within the brainstem in producing the ultradian rhythm of sleep (Hobson et al., 1975; McCarley, 2004). More recent neurophysiological studies revealed the leading role of ventrolateral periaqueductal gray and dorsal paragigantocellular reticular GABAergic nuclei in driving this interaction and producing ultradian sleep cycles (Luppi et al., 2012).

6.2. Indexing the ultradian rhythmicity of NREM-REM alternation: classic measures

The commonly used consensual rules of staging polysomnography records according to the R&K and AASM criteria (see Table 1) provide us with a rough picture of ultradian sleep regulation: the number and the length of sleep cycles, as well as their regularity is in fact reflected in the hypnogram. Specific sets of rules applied to staged sleep records clarifying ultradian sleep cycle boundaries were put forward (Feinberg and Floyd, 1979) and adapted or specified in later reports (Aeschbach and Borbély, 1993; Tarokh et al., 2011). It is obvious that sleep staging-based definition of ultradian sleep cycles has its own merits, constituting the classical way of approaching the issue. However, the basis of this definition suffers from all caveats of rule-based sleep scoring, which were already mentioned before (Lim et al., 2020; Stanley, 2023).

Studies relying on the overnight dynamics of band-limited or binwise spectral EEG measures successfully reproduce the cyclic recurrence of increased SWA/delta power in NREM sleep phases, as well as the dampening of these measures in REM phases (Aeschbach and Borbély, 1993). Detailed binwise spectral analyses of state transitions revealed a change in power density over practically the entire frequency range: high delta and sigma activity, as well as low beta power were revealed for both initial and final periods of NREM sleep (S2–S4) compared to S1 and REM, respectively (Aeschbach and Borbély, 1993). The Neuronal Transition Probability Model is one of the most elaborated approaches of this kind and relies on sequential and interdependent changes in the relative predominance of beta, sigma and delta band power values, defining the dynamics of ultradian sleep cycles (Merica and Fortune, 1997). The model successfully integrates ultradian regulation with neuronal activity (Merica and Fortune, 2004) and circadian regulation (Merica and Fortune, 2011). Although well-elaborated, this model and the other EEG power-based approaches inherently conflate ultradian regulation and sleep homeostasis, as EEG power is a strong indicator of the latter process as well.

Besides sleep scoring and band-limited EEG spectra the analysis of the EOG signal provides us with a further potential insight into the presence or absence of an actual REM stage, thus the recurrent emergence of episodes with rapid eye movements indicates the ultradian periodicity of NREM-REM alternation (Hilbert and Naitoh, 1972). Indeed, wakefulness is characterized by eye movements as well, thus, the distinction between REM and wake states is difficult when relying on this measure. Furthermore, rapid eye movement density during REM sleep was shown to reflect sleep homeostasis as well (Aserinsky, 1969, 1973; Barbato et al., 1994; Marzano et al., 2011). As a result, early REM phases of sleep might contain a low number of scarcely detectable eye movements, especially in conditions of high homeostatic sleep pressure.

6.3. Indexing the ultradian rhythmicity of NREM-REM alternation: looking at the spectral exponent of the EEG

The formerly presented, wide-range EEG power redistributions during the process of transitioning toward or away from the NREM phase of sleep (Aeschbach and Borbély, 1993; Merica and Fortune, 1997) as well as the sleep stage-based differences in the spectral exponent (Miskovic et al., 2019; Schneider et al., 2022) suggest that the steepness of the EEG spectra follows an ultradian rhythm. Indeed, the time series of spectral slopes were shown to descend and ascend cyclically across a night such that the troughs of the time series coincide with non-REM sleep while the peaks of these time series coincide with REM sleep. Based on this observation the concept of “fractal cycles” of sleep has been introduced as a measure of ultradian rhythmicity of NREM-REM alternations (Rosenblum et al., 2023 a). A typical night sleep consists of 4–6 fractal cycles which last for approximately 90 minutes, a description that strikingly resembles that for classical NREM-REM cycles. Interestingly, children and adolescents as well as older healthy adults show shorter fractal cycles as compared to young healthy adults (inverted U-shape as a function of age), whereas medicated patients with depression showed longer fractal cycles compared to their own unmedicated state and healthy controls (Rosenblum et al., 2023 a). Moreover, the fractal cycle algorithm reliably detects the so-called “skipped” cycles, the cycles where only a “lightening of sleep” occurs and no REM sleep is observed, possibly due to too high non-REM sleep pressure (Le Bon, 2020). This is a very important methodological strength of this approach, which might help in, for example, REM sleep behaviour disorder as a means to more easily detect REM sleep without atonia episodes, which currently, are often mistaken as non-REM sleep. In sum, these recent findings suggest that spectral slopes-based “fractal cycles” of sleep can measure ultradian rhythmicity of NREM-REM alternations.

6.4. Indexing the ultradian rhythmicity of NREM-REM alternation: recurrent and abrupt shifts in oscillatory peak frequencies

Unequivocal evidence supports the specificity of the emergence of sleep spindle oscillatory peak frequencies to the EEG spectra of the NREM phases of sleep. The already mentioned characteristic emergence of spindle frequency spectral peak or peaks in the NREM (N2 and N3) periodogram (Jobert et al., 1992) seems to be particularly specific to the mentioned sleep phase (stages). The earliest reports comparing R&K sleep stages or NREM and REM phases revealed a peak or a transient cessation in the monotonously decreasing power along the frequency axis at the spindle frequency in R&K stages 2–4 sleep, but not REM, stage 1 or wakefulness (Borbély et al., 1981; Dumermuth et al., 1983).

Moreover, wake to NREM sleep transitions were evidently characterized by the emergence of the spectral peak in the spindle range, whereas NREM to REM phase transitions are related to disappearance of that peak (Aeschbach and Borbély, 1993). Likewise the parametrization of sleep EEG spectra indicates the confinement of maximal spectral peak frequencies to NREM sleep periods including AASM stages N2 and N3, but not N1, whereas wakefulness and REM sleep are largely characterized by spectra peaking in the non-spindle ranges, the latter covering the theta, alpha or beta domains (Schneider et al., 2022). The ubiquity of this finding suggests that distinct oscillatory categories define distinct phases of the ultradian sleep cycles. As a consequence, sleep is not only a more or less smooth fluctuation in EEG SWA/delta power or spectral exponent at the ultradian, roughly 90 minutes rate, but also a recurrent and abrupt shift between spindle and non-spindle oscillatory modes of the cortex.

7. Reconsidering the two-process model of sleep regulation in terms of fractal and oscillatory spectra

7.1. Sleep EEG spectral exponents and peak frequencies as indicators of homeostatic, circadian and ultradian sleep regulatory processes

In coherence with the core theses of the two-process model, homeostatic timekeeping and circadian timing are crucial factors in the regulation of sleep propensity and intensity in humans and other mammals (Borbély, 1982; Borbély et al., 2016). Overwhelming evidence suggests that there are two types of brain activity that coexist: the broadband, aperiodic activity and the narrow-band, rhythmic oscillations (He, 2014). The conceptual framework presented herein is largely based on this latter distinction. The proposal is based on the following claims:

1. sleep homeostasis is reflected by the spectral exponent, a composite measure of the dominance of lower over higher frequency EEG: steeper slopes indicate higher sleep propensity (accumulated sleep need).
2. circadian regulation of sleep is reflected by the oscillatory frequency of sleep spindles, with a U-shaped overnight dynamic, the deceleration period indicating a biological night.
3. ultradian regulation of sleep consists of abrupt and recurrent shifts in dominant resonance oscillatory frequency of the EEG, where spindle frequency oscillations indicate the presence of NREM phases, whereas their replacement by theta or beta waves reveals REM phase; in addition, ultradian regulation is indexed by the time series of fractal spectral slopes.

The EEG spectral exponent can be defined in terms of a normal range, unlike SWS/N3 amount or SWA. We think that the chances to fill the gap in the knowledge on normative sleep parameters are increased by assuming that the decreased (more negative) spectral exponent is the standardisable effector response of the central nervous system during sleep. In addition to the attractive option for dealing with the gap between basic sleep science and somnology, the focus on the spectral exponent could provide us with further, albeit theoretical advantages. Our proposal to assess sleep in terms of the departure of the EEG spectral exponent from the critical value of $\alpha = -2$, fluctuating in the form of fractal cycles, might deepen our understanding of the studies focusing on the function of sleep or on the nature of conscious awareness. Moreover, the core of the present hypothesis (i) is a conceptual change in the focus or the nature of the homeostatic effector mechanism per se. Instead of hypothesizing a leading role of the slow oscillation and or delta wave activity in the dissipation of sleep need, the present assertion suggests that it is rather the aperiodic, non-oscillatory dynamics of the time series which plays a major role. Lower spectral exponents, indicating steeper spectral slopes, reflect a statistical tendency of increasing membrane hyperpolarization in neural network elements to be followed by further increases in hyperpolarization, whereas increases in depolarization are followed by further increases in depolarization. This is called neuronal bistability in classical neurophysiological terms and persistent fractional Brownian motion in the science of statistical fractals. Obviously, this hypothesis does not contradict the involvement of specific slow oscillatory mechanisms in sleep homeostasis but we have to consider that sleep is local (Krueger et al., 2008). Thus in the scalp EEG, we detect the summation of potentials of various local neural assemblies, which are averages and aggregates of basically uneven processes. As a consequence, clear limits between the up-down states of the slow oscillation are usually not always discernible in the EEG nor can we be sure if the actually measured deflection is an oscillatory or aperiodic element of the EEG. Indeed, the presence of a spectral peak (upward deflection above the levels predicted by the underlying power law) can indicate an oscillation. It remains to be determined if whitened spectral peaks of the slow oscillation/delta activity as measured by whitened spectral peak sizes, play specific roles in the process of sleep homeostasis or are indeed parts of the same mechanism we put implicitly forward in this theoretical context. In short, we propose that wakefulness implies an antipersistent type of EEG dynamics, characterized by a spectral exponent of $\alpha > -2$. In this state, increases in hyperpolarization are typically followed by decreases in hyperpolarization. The same holds true for depolarization. The longer (and perhaps the stronger, the latter meaning higher α values) this dynamical property is maintained, the higher the need to change to persistent fractional Brownian motion, characterized by steep spectral slopes already characterized above. This assumption fits with reported evidence suggesting that the task-specific EEG spectral exponents capture focal attention-related changes in E:I brain state (Waschke et al., 2021), whereas tasks that require more attention drive sleep need and sleep intensity (Kirszenblat and van Swinderen, 2015). In addition to the above considerations, the present concept is coherent with the recently proposed reciprocal dynamic of reactive and predictive homeostasis during sleep (Simor et al., 2023). Steeper fractal spectra (G. Horváth et al., 2022) and deeper fractal cycles (Rosenblum et al., 2023 a) seen during the early night sleep could reflect intensive restorative processes (which are also reflected by SWA), whereas flatter fractal slopes/shallower fractal cycles seen during the later part of night's sleep could reflect more active future-oriented processes, characterized by relatively higher cognitive load and a shift towards neural excitation relative to inhibition.

SWA was proposed to vary between the upper and the lower limits defined by the circadian phase in the detailed, mathematically formulated version of the two-process model of sleep regulation (Daan et al., 1984). Here we proposed that the underlying circadian phase is indicated by the oscillatory frequency of sleep spindles. Further work is needed to determine the mathematically precise and physiologically meaningful relationship between the fast and slow sleep spindle frequencies and the upper and lower limits of Process, respectively. Indeed, the evidence for the relationship between oscillatory sleep spindle frequency and circadian modulation is strong.

The two-process model parametrized the ultradian oscillation as an autonomous rhythm generator as described by the reciprocal interaction model, but gated by process (Borbély, 1982). This coheres with the current proposal of the oscillatory peak frequency as being the common denominator of circadian and ultradian regulation of sleep. While Process is proposed to be indexed by slow drifts in oscillatory sleep spindle frequency, ultradian regulation is modelled by the recurrent and abrupt shifts in the oscillator, leading to a rapid departure from the canonical sigma range and fluctuations in the steepness of the fractal slopes. Further studies need to clarify if the ongoing and Process -reflecting oscillatory spindle frequency is indeed an empirically testable modulator of REM initiation tendencies. Specifically, we need to unravel if spindle oscillatory frequencies are predictors of the transition into the REM phase of sleep or modulators of REM duration.

Based on the physiologically and empirically meaningful decomposition of the EEG time series into fractal and oscillatory spectral

measures we put forward the basic elements of a renewed conceptual framework of sleep regulation. The proposed name of this framework could be termed as the Fractal and Oscillatory Adjustment Model (FOAM) of sleep regulation (Fig. 5).

7.2. *Is FOAM somnologically meaningful: clinical relevance of the revised two-process model of sleep regulation?*

7.2.1. *Revisiting the S-deficiency hypothesis of major depressive disorder*

Within the context of the very first clinical application of the two-process model of sleep regulation, authors aimed to model the sleep alterations of patients suffering from major depression, by assuming a reduced level of Process S in this psychiatric condition (Borbély and Wirz-Justice, 1982). Given the conceptual and predictive validity of the S-deficiency hypothesis of depression (Borbély, 1987; Macher et al., 2004), any alternative index of sleep homeostasis is expected to provide us with a similar group difference between depressed and non-depressed subjects (discriminative validity). Indeed, stage N2 sleep EEG spectral slopes were examined and reported to indicate flatter spectral decay in patients diagnosed with major depressive disorder as compared to healthy control participants (Rosenblum et al., 2023 b). Such findings maintain the creative potential of the S-deficiency hypothesis of depression, but might open further avenues in understanding the nature of sleep alterations in patients suffering from mood disorders.

In addition to discriminative validity, the FOAM of sleep regulation resolves the apparent contradiction between the gender differences in the prevalence of major depressive disorder and sleep EEG SWA. Specifically, the incidence of depression is significantly higher in women as compared to men (Albert, 2015), while in terms of SWA, the gold standard measure of Process S, women are consistently characterized by higher values, the latter suggesting deeper sleep (Carrier et al., 2001; Dijk, Beersma, and Bloem, 1989). In spite of the intriguing gender differences in rebound sleep after extended wakefulness in patients with major depression (Armitage and Hoffmann, 2001), the findings on the baseline differences contrast the prediction of the S-deficiency hypothesis. Indeed, the new sleep homeostatic measure put forward in the FOAM of sleep regulation, namely the EEG spectral exponent was not revealed to differ significantly among women and men (Bódizs et al., 2021). Although, the potential role of sex hormones in mood disorders is still an important issue (Albert, 2015), the equality of spectral exponents among the sexes leaves space for these effects.

7.2.2. *Flatter EEG spectra and more alpha peaks in insomnia and sleep state misperception*

Patients suffering from chronic insomnia or sleep state misperception, both characterized by fragility of sleep and sleep-related conscious awareness, were revealed to express flatter stage N2 and N3 sleep EEG spectral decay as compared to good sleeper controls (Andrillon et al., 2020). The typical finding of increased high-frequency sleep EEG activity in insomnia sufferers, as well as the occasionally reported, but not

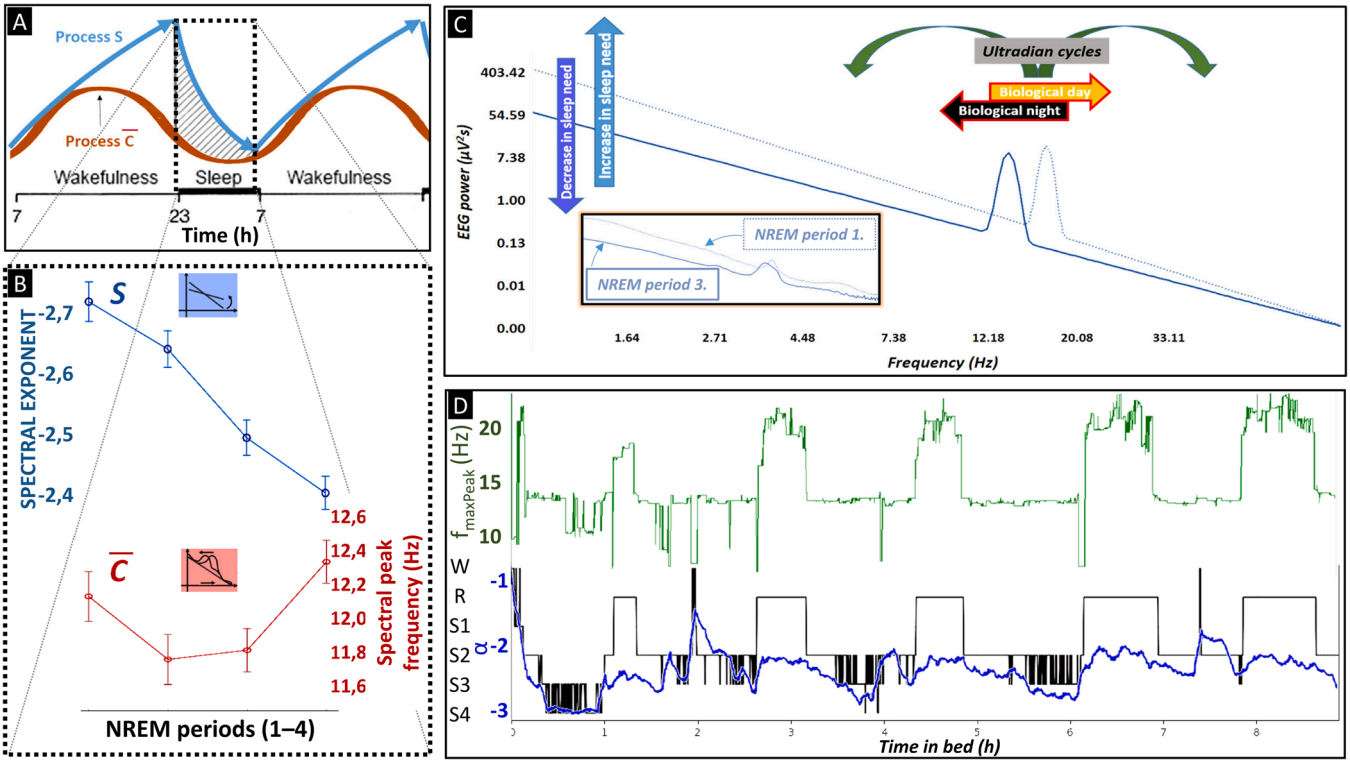


Fig. 5. From the two-process model to the Fractal and Oscillatory Adjustment Model (FOAM) of sleep regulation. A. The two-process model of sleep regulation adapted from (Borbély, 1982). B. The correspondence between Process S and the spectral exponent, as well as Process and the spectral peak frequency in the spindle range. Data are based on the left frontopolar recording locations (Fp1-A1A2) of N = 251 subjects (age range: 4–69 years, 122 females) and adapted from (G. Horváth et al., 2022). C. Depicting the spectral picture of FOAM in double logarithmic coordinates: model and empirical example (insert figure). The latter depicts the power spectral densities of the fronto-frontal recording (F7-Fpz) performed by the usage of a mobile sleep recording headband (Hypnodyne Zmax) in NREM period 1 (dotted line) and 3 (continuous line). Note, the flattening of spectral decay is assumed to reflect decreased homeostatic sleep pressure, as well as the deceleration in spindle peak frequency (assumed to indicate circadian regulation/biological night). D. Ultradian sleep regulation as indexed in the FOAM. Maximal peak frequency ($f_{maxPeak}$, green) in the whitened spectra (power law scaling removed) as expressed in moving averages of 75 consecutive, 4 s long, Hanning-tapered segments (overlap 74×4 s) of left central (C3-A1A2) recording location of a healthy male volunteer (age: 20 years). The recording was intentionally not de-artefacted before the analysis in order to emphasize usability in everyday practice. An overplot of $f_{maxPeak}$ and the spectral exponent (α, blue) with the R&K-staged hypnogram is a proof for an excellent correspondence between ultradian NREM-REM cycles and recurrent, abrupt departures of fmaxPeak far above the spindle range. In addition, rhythmic changes in the spectral exponent α cohere with ultradian cycles and transient awakenings during the night.

always revealed decrease in NREM sleep EEG delta power (Zhao et al., 2021) suggests that band-limited power differences among insomnia patients and good sleepers could indeed reflect the alterations in spectral slope steepness of the former group. Thus, the spectral exponent is a simple, composite and non-redundant measure indicating central nervous system and/or cognitive hyperarousal in insomnia/sleep state misperception patients.

Intriguingly, greater sleep complaints and a higher prevalence of insomnia disorder in women are not reflected in objective sleep parameters. The latter indicates higher SWS/N3 sleep and SWA in women as compared to men, "suggesting that objective and subjective assessments tap into different constructs of sleep" (Baker et al., 2023). However, the sharp contradiction between subjective and objective sleep quality could be partially attenuated by relying on the spectral exponent instead of SWA, as the former was shown to be characterized by equal values in women and men (Bódizs et al., 2021).

We provide a re-analysis of an open database on psychophysiological insomnia and control subjects (N = 11 subjects in each group) in Fig. 4. C, D (Rezaei et al., 2017). Aggregated slopes derived from sequential fits to instantaneously changing moving average EEG spectra highlight the above mentioned difference in spectral exponents (i.e. more frequent episodes of flatter spectral slopes in insomnia records, Fig. 4. C), whereas oscillatory peak frequencies redistribute from spindle to alpha oscillations (Fig. 4. D). The latter finding coheres with reports suggesting that EEG alpha activity can be considered as an index of arousal during sleep (Halász et al., 2004; McKinney et al., 2011; Pivik and Harman, 1995; Simor et al., 2013).

7.2.3. Steeper spectral slopes in NREM parasomnia disorders

In contrast to the findings reported in insomnia subjects, NREM sleep parasomnia disorders (sleep-related eating disorder, sleepwalking, sleep terrors, and confusional arousals) are known to be indexed by transient episodes of unusually high amplitude slow EEG waves during NREM sleep, leading to dissociated arousal responses (Camaioni et al., 2021). In coherence with the present conceptual framework, patients diagnosed with NREM parasomnia were revealed to be characterized by lower N3 sleep EEG spectral exponents (steeper slopes) as compared to a group of sleep-related hypermotor epilepsy patients, characterized by partially overlapping symptoms, but different aetiologies (Pani et al., 2021). Thus, microstructural alterations specific to NREM parasomnia might be detectable by reliance on the sleep EEG spectral exponent (slope steepness).

7.2.4. Accelerated oscillatory spindle frequency - I: an index of circadian dysregulation in Williams syndrome?

Mistimed sleep or disrupted circadian rhythms are alternative causes of sleep insufficiency. Although the direct evidence supporting the reliability of the measures of sleep spindle frequency in clinical conditions characterized by alterations of the circadian rhythm is scarce, some indirect findings are suggestive in this regard. Williams syndrome (also called as Williams-Beuren syndrome), a neurodevelopmental disorder caused by microdeletion of 25–27 genes on the chromosomic region 7q11.23 (Kozel et al., 2021) and characterized among others by significant alterations in sleep quality (Bódizs, Gombos, Gerván, et al., 2014; Gombos et al., 2011), was shown to be associated with a less pronounced increase in melatonin release at bed time (Sniecinska-Cooper et al., 2015). Indeed, Williams syndrome subjects were shown to express an overall increase in sleep spindle frequency as compared to their age- and sex-matched, typically developing peers (Bódizs et al., 2012; Bódizs, Gombos, Szocs, et al., 2014). The overnight dynamics of oscillatory sleep spindle frequency has to be determined, but higher mean values resemble daytime sleep or the lack of sufficient circadian modulation (night time deceleration), perhaps related to reduced melatonin levels. In addition, accelerated sleep spindle frequencies associate with non-continuous sleep in these groups of subjects.

7.2.5. Accelerated oscillatory spindle frequency - II: an index of circadian dysregulation in post-traumatic stress disorder?

Disruption of circadian clocks often represents a hallmark of several neuropsychiatric disorders rooted in prenatal/early-life insults (Marco et al., 2015) or traumatic stress suffered during adulthood (Agorastos and Olff, 2020). Indirect evidence supporting the relationship between assumed circadian dysregulation, sleep insufficiency and increased oscillatory sleep spindle frequency comes from studies conducted on post-traumatic stress disorder patients. Posttraumatic chronodisruption was shown to represent a core feature of trauma-related disorders mediating enduring neurobiological correlates of traumatic stress and leading to a breakdown of biobehavioral adaptive mechanisms (Agorastos and Olff, 2020). Besides reporting evidence supporting the elevated oscillatory sleep spindle frequency in this psychiatric condition (Denis et al., 2021; Wang et al., 2020), authors revealed correlations between the acceleration of sleep spindles and the symptoms of sleep alteration, including the occurrence rate of arousals during sleep (Wang et al., 2020).

7.3. FOAM in a comparative perspective: nocturnality, extreme environments and avian sleep

Rodents are frequently used model species in sleep research. Empirical evidence suggests that the Fourier spectra of rodent EEG records follow a power law scaling (Magyar et al., 2023; F. Zhang et al., 2019). Preliminary findings in mice indicate that EEG spectral slope steepness reflects increases in sleep intensity after stress (Jász et al., 2023) and following periods of extended wakefulness (Magyar et al., 2023). Furthermore, steepening of the rat sleep EEG spectral slope was evidenced in post-stroke periods (Leemburg et al., 2018), an EEG-feature which is peculiar to human clinical samples as well (Lanzone et al., 2022).

In contrast to the apparent steadiness of sleep homeostasis in most of the mammalian species analysed in common settings, there are several experimentally supported examples for dynamically changing sleep homeostatic set points in some aquatic mammals, like the northern elephant seals (Mirounga angustirostris) (Kendall-Bar et al., 2023), reindeer in the arctic (Rangifer tarandus tarandus) (Furrer et al., 2024) and several avian species. Indeed, the evidence for avian sleep homeostasis is much more conflicting. Reported examples are the significant and largely uncompensated reductions in uni- and bihemispherical sleep amounts during migratory behaviour of great frigatebirds (Fregata minor) (Rattenborg et al., 2016), the curtailment of sleep by lengthened light phases in European jackdaws (Coloeus monedula) (Van Hasselt et al., 2023), or the season-specific attenuation in the reactions to homeostatic challenges of sleep in barnacle geese (Branta leucopsis) (Van Hasselt et al., 2021). Whereas the above examples might indicate the flexibility of the set point of the sleep homeostat in at least some avian species, other findings indicate the similarity of avian and mammalian sleep homeostasis. Likewise, the analysis of the EEG of white-crowned sparrows (Zonotrichia leucophrys) revealed a clear homeostatic behaviour characterized by sleep-time-dependent decline and sleep deprivation-induced increase in SWA. It is remarkable that excess EEG power recorded during recovery sleep of white-crowned sparrows extended beyond SWA and levelled off with increasing frequencies (S. G. Jones et al., 2008), as did excess sleep EEG power in the ipsilateral hemisphere of unihemispherically sleep deprived pigeons (Columba livia) (Lesku et al., 2011). Together with reports on apparent power law scaling of the EEG spectra in zebra finches (Taeniopygia guttata) anesthetized with isoflurane, these types of evidence are suggestive for a convergence of the functions of sleep in mammals and birds. Altogether the overall landscape of avian sleep homeostasis is still controversial, and the evidence for the involvement of fractal neurodynamics in this process is largely based on scarce and indirect data. Well-designed future studies or reanalyses of existing avian EEG-data could clarify the above issue. Remodelling the process in the context of FOAM could

paw the way toward the understanding of the peculiarities of avian sleep homeostasis.

To the best of our knowledge there is no published data on the circadian variation of oscillatory sleep spindle frequencies in rodents. Although, the positive correlation between (locally manipulated) brain temperature and oscillatory sleep spindle frequency was evidenced in mice (Csernai et al., 2019), the diurnal pattern of core body temperature is a complex issue, given the prevailing nocturnality in rodent species. In contrast to diurnal species, which were shown to lower their core body temperature in response to melatonin treatment (Dawson et al., 1996; Schwimmer et al., 2010), nocturnal rodents reacted to exogenous melatonin by hyperthermia (Huber et al., 1998). As a consequence, melatonin release and the circadian nadir in core body temperature are out of phase in nocturnal species (Challet, 2007). It remains to be determined if sleep spindle frequencies fluctuate in synchrony with core body temperature or rather with melatonin in nocturnal rodents. This would then define the way of modelling sleep regulation of nocturnal mammals in the context of FOAM (that is, by preferred sleep periods at the nadir or the crest of sleep spindle frequencies). A further intriguing open issue is the circadian rhythm in polar vertebrates. Data on electrical brain activity-related circadian indices could reveal the peculiarities of the species characterized by maintained persistent rhythmicity in constant environmental light conditions. This persistence was suggested to be adaptive due to interdependence between circadian clock function and homeostatic processes (Williams et al., 2015).

Neither spontaneous, nor benzodiazepine-altered sleep recordings resulted in revealing sleep spindles in avian species studied so far (Van Der Meij et al., 2019). The lack of a spindle frequency spectral peak in avian sleep EEG constitutes a major challenge in applying the herein proposed version of FOAM to explain and describe bird sleep regulation. The peculiar presence of multiple, interconnected circadian pacemakers in birds, including the pineal gland and the retinae besides the suprachiasmatic nuclei (Cassone, 2014), as well as the strong dependence of avian sleep on external light (Aulsebrook et al., 2021) might be at the basis of these divergences and inconsistencies between the animal classes. Future studies focusing on the circadian phase- and environmental light-dependent aspects of avian electrophysiology could shed light on sleep spindle-equivalent EEG measures of birds, which could substitute the neurophysiological machinery of thalamic gating in the mammalian version of FOAM presented herein.

8. Conclusion: toward the abandonment of sleep staging

Sleep is a complex process probably evolving from a metabolically quiescent rest state and constituting a fundamental property of neuronal assemblies (Krueger et al., 2008). The detailed and comprehensive discussion of the multitudinous molecular, neurochemical and neural factors of sleep regulation is beyond the scope of the present paper. As a consequence, some of the biochemical and neurological explanations we put forward might look a bit over-simplistic, and should be specified in future works focusing on FOAM. Instead of a molecularly rooted model we opted for a synthesis of core findings on collective, state-dependent neuronal dynamics and the reframing of fundamental regulatory processes of sleep and wakefulness. We also aimed to explicitly reflect on the issue of objective sleep measurement in human subjects, which we considered critical in constructing new theories or models.

Staging of sleep records on the basis of consensual rules is a more than eight decades old practice (see the timeline highlighted in Table 1). Although, the approach is deeply rooted in the era of paper-based (non-digital) polysomnography, it is still considered as a gold standard method of evaluating sleep. Without disputing the extraordinary importance of the procedure in historical terms, we agree with the views expressing the need for a renewal in the human scorer-dependent, consensual rule-based approach (Stanley, 2023). The distinction between fractal (aperiodic, scale-free) and oscillatory spectra could constitute a basis of this reframing. This could provide us with the option of tracking fundamental sleep regulatory processes in the clinical practice, leading to a fruitful synthesis of academic sleep research concepts and sleep medicine. One such potentially reframing approach would be the recently proposed spectral slope-based concept of fractal cycles of sleep (Rosenblum et al., 2023 a). Circumstantial evidence suggests that the spectral exponent of human EEG is a promising and reliable measure of sleep homeostasis or sleep intensity, reflecting sleep-wake history, sleep stage differences, sleep cycles, age-effects, local sleep and sleep disorders. The spectral exponent determines the power law of the overall frequency-dependent decay of EEG power and equals the spectral slope in double logarithmic coordinates. Potential sources of specific spectral exponent values might stem from the E:I ratio of the central nervous system, as well as the bistability of the network (the overall tendency of alternating up and down states). Moreover, some well characterized neurochemical regulatory factors of wake and sleep states, like noradrenaline and acetylcholine, were shown to modulate the steepness of spectral slopes. Last, but not least spectral exponents provide us with a measure of sleep intensity which is promising in terms of comparability of individual records, increasing the plausibility of establishing clear reference values.

Circadian rhythms were usually not assessed from polysomnography or EEG measures of sleep. Indeed, evidence from various sources suggests that the oscillatory frequency of sleep spindles follows a circadian modulation. Both slow and fast sleep spindles seem to decelerate in the middle of the night period, following a U-shaped overnight dynamic. Although the deceleration is usually limited to a few tenths of Hz (up to a 0.5 Hz day vs night difference), it could provide us with a promising measure of the circadian modulation strength and phase. Results on this measure successfully reproduce predicted age-effects and cohere with both the temperature-dependence of biological oscillators and the putative effects of melatonin on the reticular thalamic nucleus.

Ultradian sleep organization is usually defined in terms of the hypnogram, the latter derived from the work of rule-based scorers of polysomnography records, involving inherent subjectivity. Our novel approach of detecting ultradian cycles of sleep relies on the fact that the maximal peak frequency in the whitened EEG spectra is characterized by recurrent and abrupt shifts made up by sudden departures from the sleep spindle frequency range. The regularity of these sudden shifts constitutes an ideal marker of the underlying state changes. The characterization of sleep can be fine-graded by the analysis of the contribution of specific spectral peak frequencies relative to all-night averages (see Fig. 4. B and D). In addition, ultradian sleep organization can be tracked with times series of spectral slopes (i.e., fractal cycles of sleep). The combination of the spectral exponent and the maximal oscillatory peak frequency of the EEG could constitute a promising new way of characterizing the overnight dynamics, as well as the clinically important features of sleep processes leading to the potential abandonment of sleep staging in future studies. Moreover, the dynamical properties of the above indicators are partially coherent with the basic assumptions of the two-process model of sleep regulation and are summarized in the context of a new putative conceptual framework termed FOAM. Indirect and preliminary evidence suggests that FOAM can be a theoretical framework with significant translational relevance in the field of sleep medicine or clinical somnology. Further research supporting this claim, as well as relevant comparative studies on avian species, as well as aquatic and nocturnal mammals are needed and are aimed to be facilitated by the theoretical framework presented above.

CRediT authorship contribution statement

Yevgenia Rosenblum: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. Martin Dresler: Conceptualization, Data curation, Funding acquisition, Supervision, Writing – review & editing. Róbert Bódizs: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing –

review & editing. Csenge G. Horváth: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Péter Ujma: Data curation, Resources, Writing – review & editing. Bence Schneider: Conceptualization, Methodology, Software, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Data Availability

Data is included in the manuscript and the Supplementary table 1.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2024.102589.

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