Fractal cycles of sleep: a new aperiodic activity-based definition of sleep cycles

Yevgenia Rosenblum[1], Mahdad Jafarzadeh Esfahani[1], Nico Adelhöfer[1], Paul Zerr[1], Melanie Furrer[2], Reto Huber[2,3], Axel Steiger[4], Marcel Zeising[5], Csenge G. Horváth[6], Bence Schneider[6], Róbert Bódizs[6], Martin Dresler[1]

[1] Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, Netherlands,

[2] Child Development Center and Children's Research Center, University Children's Hospital Zürich, University of Zürich, Zürich, Switzerland,

[3] Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zurich, Zurich, Switzerland,

[4] Max Planck Institute of Psychiatry, Munich, Germany,

[5] Klinikum Ingolstadt, Centre of Mental Health, Ingolstadt, Germany,

[6] Semmelweis University, Institute of Behavioural Sciences, Budapest, Hungary

Corresponding author: Yevgenia Rosenblum, e-mail: yevgenia.rozenblum@donders.ru.nl

Abstract

Nocturnal human sleep consists of 4 – 6 ninety-minute cycles defined as episodes of non-rapid eye movement (non-REM) sleep followed by an episode of REM sleep. While sleep cycles are considered fundamental components of sleep, their functional significance largely remains unclear. One of the reasons for a lack of research progress in this field is the absence of a "data-driven" definition of sleep cycles. Here, we proposed to base such a definition on fractal (aperiodic) neural activity, a well-established marker of arousal and sleep stages.

We explored temporal dynamics of fractal activity during nocturnal sleep using electroencephalography. Based on the observed pattern of fractal fluctuations, we introduced a new concept, the "fractal" cycle of sleep, defined as a time interval during which fractal activity descends from its local maximum to its local minimum and then leads back to the next local maximum. Next, we assessed correlations between "fractal" and "classical" (i.e., non-REM – REM) sleep cycle durations. We also studied cycles with skipped REM sleep, i.e., the cycles where the REM phase is expected to appear except that it does not, being replaced by "lightening" of sleep.

Regarding the sample, we examined fractal cycles in healthy adults (age range: 18 – 75 years, n = 205) as well as in children and adolescents (range: 8 – 17 years, n = 21), the group characterized by deeper sleep and a higher frequency of cycles with skipped REM sleep. Further, we studied "fractal" cycles in major depressive disorder (n = 111), the condition characterized by altered REM sleep (in addition to its clinical symptoms).

We found that "fractal" and "classical" cycle durations (89 ± 34 min vs 90 ± 25 min) correlated positively ($r = 0.5$, $p < 0.001$). Cycle-to-cycle overnight dynamics showed an inverted U-shape of both fractal and classical cycle durations and a gradual decrease in absolute amplitudes of the fractal descents and ascents from early to late cycles.

In adults, the "fractal" cycle duration and participant's age correlated negatively ($r = -0.2$, $p = 0.006$). Children and adolescents had shorter "fractal" cycles compared to young adults (76 ± 34

vs 94 ± 32 min, $p < 0.001$). The fractal cycle algorithm detected cycles with skipped REM sleep in 53/55 (96%) cases.

Medicated patients with depression showed longer "fractal" cycles compared to their own unmedicated state (107 ± 51 min vs 92 ± 38 min, $p < 0.001$) and age-matched controls (104 ± 49 vs 88 ± 31 min, $p < 0.001$).

In conclusion, "fractal" cycles are an objective, quantifiable, continuous and biologically plausible way to display sleep neural activity and its cycles. They are useful in healthy adult and pediatric populations as well as in patients with major depressive disorder. "Fractal" cycles should be extensively studied to advance theoretical research on sleep structure.

Keywords: sleep cycles, non-REM-REM sleep cycle, aperiodic activity, 1/f function, power law, fractal power component, sleep, EEG, polysomnography, hypnogram, major depressive disorder, antidepressants, development, children and adolescent sleep.

Highlights

- The fractal sleep cycle is a new concept based on cyclic changes in fractal (aperiodic) neural activity during sleep.
- Durations of fractal and classical cycles correlate, and both show an inverted U-shape when seen from early to late cycles.
- The fractal cycle algorithm is effective in detecting cycles with skipped REM sleep.
- Older healthy adults shower shorter "fractal" cycle durations.
- Fractal cycle duration is shorter in children and adolescents compared to young adults.
- In major depressive disorder, antidepressant medication is associated with longer fractal cycles.

Introduction

The cyclic nature of sleep has long been established with a classical sleep cycle defined as a time interval that consists of an episode of non-rapid eye movement (non-REM) sleep followed by an episode of REM sleep (Feinberg & Floid, 1979; Le Bon, 2020). Typically, nocturnal sleep consists of 4 – 6 such cycles, which last for about 90 minutes each. Every cycle is seen as a fundamental physiological unit of sleep central to its function (Feinberg, 1974) or a miniature representation of the sleep process (Le Bon, 2002).

Basic structural organization of normal sleep is rather conservative with some exceptions. Thus, sometimes, especially at the beginning of the night in healthy adolescents and young adults, there could occur cycles with skipped REM sleep, which are sometimes also called “skipped” cycles. In skipped cycles, a REM sleep episode is expected to appear except that it does not and only a “lightening" of sleep is observed presumably due to too high non-REM pressure (Le Bon, 2020). Likewise, some alterations of the sleep structure can be observed in sleep disorders, e.g., narcolepsy and insomnia (Scammell, 2015), and healthy aging (Carrier et al., 2011; Conte et al., 2014). In some neurological and psychiatric conditions, such as major depressive disorder (MDD), Parkinson’s and Alzheimer’s diseases, sleep architecture disturbances are further linked to the disease neuropathology (Courtet & Olié, 2012; Palagini et al., 2013; Pillai & Leverenz, 2017).

While the importance of sleep cycles is indisputable, their function as a unit is poorly understood and surprisingly under-explored, especially when compared to the extensive research on sleep stages (either non-REM or REM) or sleep microstructure (e.g., sleep spindles, slow waves, microarousals). One of the reasons for this striking absence of research progress might be the lack of proper quantifiable and reliable objective measure from which sleep cycles could be derived directly (Schneider et al., 2022).

Currently, sleep cycles are defined via a visual inspection of the hypnogram, the graph in which categorically separated sleep stages are plotted over time. Sleep stages, however, are continuous and do not occur as steep lines of a hypnogram. Therefore, assigning a discrete

category to each sleep stage is rather arbitrary, has little biological foundation and disregards gradual aspects of typical biological processes (e.g., gradual nature of circadian hormone fluctuations, growth and development). In addition, visual sleep stage scoring is very time-consuming, subjective and error-prone with a relatively low (~80%) inter-rater agreement. This results in a low accuracy regarding the sleep cycle definition.

We suggest that a data-driven approach based on a real-valued neurophysiological metric (as opposed to the categorical one) with a finer quantized scale could forward the understanding of sleep cycles considerably. Specifically, we propose that research on sleep cycles would benefit from recent advances in the field of fractal neural activity. In literature, fractal activity is also called aperiodic, non-oscillatory, 1/f or scale-free activity, being named after the self-similarity exhibited by patterns of sensor signals across various time scales. Fractal activity is a distinct type of brain dynamics, which is sometimes seen as a "background" state of the brain, from which linear, rhythmic (i.e., periodic, oscillatory) dynamics emerge to support active processing (Buzsaki, 2006; Freeman et al., 2006). Growing evidence confirms that fractal activity has a rich information content, which opens a window into diverse neural processes associated with sleep, cognitive tasks, age and disease (Voytek & Knight, 2015; Bódizs et al., 2021; 2023; Höhn et al., 2022).

Fractal dynamics follow a power-law 1/f function, where power decreases with increasing frequency (He, 2014). The steepness of this decay is approximated by the spectral exponent, which is equivalent to the slope of the spectrum when plotted in the log-log space (He, 2014; Gerster et al., 2022). The fractal signal is not dominated by any specific frequency, rather it reflects the overall frequency composition within the time series (Horváth et al., 2022) such that steeper (more negative) slopes indicate that the spectral power is relatively stronger in slow frequencies and relatively weaker in faster ones (He, 2014).

In terms of mechanisms, it has been suggested that flatter high-band (30 – 50Hz) fractal slopes reflect a shift in the balance between excitatory and inhibitory neural currents in favour of excitation while steeper slopes reflect a shift towards inhibition (Gao et al., 2017). Given that the specific balance between excitation and inhibition defines a specific arousal state and the

conscious experience of an organism (Nir & Tononi, 2010), the introduction of Gao's model led to an increased interest in fractal activity. For example, it has been shown that high-band fractal slopes discriminate between wakefulness, non-REM and REM sleep stages as well as general anesthesia or unconsciousness (Gao et al., 2017; Colombo et al., 2019; Lendner et al., 2020; Höhn et al., 2022).

Of note, Gao's model does not account for the lower part of the spectrum, which is also scale-free. An alternative model suggests that the broadband $1/f^2$ activity reflects the tendency of the central nervous system to alternate between UP- (very rapid spiking) and DOWN- (disfacilitation, no activity) states (Milstein et al., 2009; Baranauskas et al., 2012). Empirical studies further showed that the broadband (2 – 48Hz) slope is an especially strong indicator of sleep stages and sleep intensity with low inter-subject variability and sensitivity to age-related differences (Miskovic et al., 2019; Schneider et al., 2022; Horváth et al., 2022). Taken together, this literature suggests that fractal slopes can serve as a marker of arousal, sleep stages and sleep intensity (Lendner et al., 2020; Schneider et al., 2022; Horváth et al., 2022). We expect that this line of inquiry could be extended to sleep cycles.

On a related note, the reciprocal interaction model of sleep cycles assumes that each sleep stage involves distinct activation patterns of inhibitory and excitatory neural networks (Pace-Schott & Hobson, 2002). This model explains alternations between non-REM and REM sleep stages by the interaction between aminergic and cholinergic neurons of the mesopontine junction (Pace-Schott & Hobson, 2002). Notably, during REM sleep, acetylcholine plays a major role in maintaining brain activation, which is expressed as EEG desynchronization, one of the main features of REM sleep (Nir & Tononi, 2010). This is of special importance in affective disorders since according to one of the pathophysiological explanations of depression, i.e., the cholinergic-adrenergic hypothesis, central cholinergic factors play a crucial role in the aetiology of affective disorders, with depression being a disease of cholinergic dominance (Janowsky et al., 1972). Many antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors) suppress REM sleep and thus cause essential alterations in sleep architecture. Intriguingly, REM sleep suppression is related to the improvement of depression

during pharmacological treatment with antidepressants enhancing monoaminergic neurotransmission (Vogel et al., 1990; Wichniak et al., 2013).

Based on this background, we propose that a fractal neural activity-based definition of sleep cycles has the potential to considerably advance our understanding of the cyclic nature of sleep, for example, by introducing graduality to the categorical concept of sleep stages. The current study analyzes the dynamics of nocturnal fluctuations in fractal activity using five independently collected polysomnographic datasets overall comprising 205 recordings from healthy adults. Based on the inspection of fractal activity across a night, we introduce a new concept and name it the "fractal activity-based cycles of sleep" or "fractal cycles" for short. We describe differences and similarities between "fractal" cycles defined by our algorithm and "classical" (non-REM – REM) cycles defined by the hypnogram. We hypothesize that the timing and durations of the "fractal" cycles would closely correspond to those of "classical" cycles. We had no prior hypothesis regarding correspondence between the fractal cycles and classical cycles with skipped REM sleep, i.e., this analysis was exploratory.

Given the above-mentioned age-related changes in fractal activity (flatter slopes) and sleep structure (fewer and shorter classical cycles), we also study whether fractal cycle characteristics change with age. To this end we use 5 healthy adult datasets with the age range of 18 – 75 years (n = 205). Moreover, we add to our study a pediatric polysomnographic dataset (age range: 8 – 17 years, n = 21) to explore fractal cycles in childhood and adolescence, a life period accompanied by deepest sleep and massive brain reorganization (Kurth et al., 2012) as well as a higher frequency of cycles with skipped REM sleep (Jenni & Carskadon, 2004).

Finally, we test the clinical value of the "fractal" cycles by analyzing polysomnographic data in 111 patients with MDD, a condition characterized by disturbed sleep structure (besides its clinical symptoms, such as abnormalities of mood and affect). Specifically, we compare fractal cycles of sleep between medicated MDD patients (three MDD datasets, n = 111) and healthy age-matched controls (n = 111) as well as in the unmedicated and medicated states within the same MDD patients (one of the three MDD datasets, n = 38). We hypothesize that the fractal

cycle approach would be more sensitive in detecting differences between typical and atypical sleep architecture compared to the conventional classical cycles.

Methods

Healthy participants

We retrospectively analyzed polysomnographic recordings from the following studies (Table 1):

Datasets 1 – 3: 40, 40 and 33 healthy controls from three independent sleep studies in MDD conducted at the Max Planck Institute of Psychiatry, Germany. These datasets are described in Rosenblum et al. (2023 a) and Bovy et al. (2022). In addition, these participants are used as controls in MDD datasets A – C described below.

Dataset 4: 36 healthy participants from a home-based sleep study exploring simultaneous polysomnographic and EEG wearables conducted at the Donders Institute for Brain, Cognition and Behavior, the Netherlands (Described as Dataset 2 in Jafarzadeh Esfahani et al., 2023). The signal was recorded at participants' homes over three nights with a gap of a week between each recording. For consistency with other datasets (i.e., to end up with a comparable number of cycles provided by each participant), we used polysomnography (and not EEG recorded by wearables) from the first night only since it had the largest sample size (i.e., 5 subjects dropped out from the study after the first polysomnographic recording).

Dataset 5: 68 healthy controls from previous endocrinological studies conducted at the Max Planck Institute of Psychiatry, Germany, using only nights with no pharmacological or endocrine intervention. 60/68 participants are described in Rosenblum et al. (2023 b).

Dataset 6: 21 healthy children and adolescents from previous studies (Furrer et al., 2019; Volk et al., 2019; Jaramillo et al., 2020) conducted at the University Children's Hospital Zürich, Switzerland. For the control group to this dataset, we selected all healthy adults from Datasets 1 – 3, 5, 6 (n = 205) whose ages lay in the range of 23 – 25 years (the age when the brain

maturation process is supposed to be finished (Giedd & Rapoport, 2010) and no age-related processes are expected to start). This resulted in 24 subjects with a mean age of 24.8 ± 0.9 years.

The studies were approved by the Ethics committee of the University of Munich (Datasets 1 – 3, 5), Radboud University (Dataset 4) and Canton of Zürich (Dataset 6). All participants (or participants' parents for Dataset 6) gave written informed consent.

Patients with MDD

We retrospectively analyzed polysomnographic recordings from our previous studies (Bovy et al., 2022; Rosenblum et al., 2023 a, Tables 1 – 2):

Dataset A: 40 long-term medicated MDD patients vs 40 age- and gender-matched healthy controls (Dataset 1 here).

Dataset B: 38 MDD patients in unmedicated and 7-day medicated states vs 40 healthy age and gender-matched controls (Dataset 2 here).

Dataset C: 33 MDD patients at 7-day and 28-day of medication treatment vs 33 healthy age and gender-matched controls (Dataset 3 here).

Demographic and sleep characteristics of the patients, medication treatment and polysomnographic devices are described in our previous works (Bovy et al., 2022; Rosenblum et al., 2023 a). Here, Supplementary Table S5 (Supplementary Material 2) presents medication treatment. In Rosenblum et al. (2023 a), Datasets A, B and C are referred to as the Replication Dataset 2, Main Dataset and Replication Dataset 1, respectively; in Bovy et al. (2022), the naming is the same as here. All studies were approved by the Ethics committee of the University of Munich. All participants gave written informed consent.

The first part of this study analyzes the data from healthy participants only and labels the datasets with the numbers 1 – 6. The second part of this study compares patients and controls and labels the analyzed datasets with the letters A – C. Notably, healthy participants used as controls in datasets A – C are the same subjects analyzed in Datasets 1 – 3.

In Supplementary Material 2, we report how many participants and for what reasons were excluded from the analysis. An example of one excluded participant is given in Fig.9 (S37).

Polysomnography

Information about the studies and polysomnographic devices is reported in Table 1. The participants slept wearing a polysomnographic device in a sleep laboratory (Datasets 1 – 3, 5, 6) or in the home environment (Dataset 4). In datasets 1 – 3 and 5 all participants had an adaptation night before the examination night; adaptation night data was not available to be analyzed and reported here. In dataset 6, all participants had two recording nights: a baseline and an examination night with auditory stimulation. Here, only the baseline night was analyzed, which was either the first night (in 50% of cases) or the second night for a given participant.

Sleep stages were previously scored manually by independent experts according to the AASM standards (AASM, 2014). In the pediatric dataset, we used 20-s epochs, in the rest of the datasets, we used 30-s epochs. Epochs with EMG and EEG artifacts and channels with more than 20% artifacts during non-REM sleep were manually excluded by an experienced scorer before all automatic analyses.

We opted to analyze the F3 and F4 electrodes for maximal consistency between the studies as these leads were available in 6 out of 7 datasets. Another reason is that in our future studies, we plan to replicate this work using the data recorded with at-home wearable devices, which often have only frontal channels (e.g., F7 and F8 only in ZMax headband, Hypnodyne Corp., Sofia, Bulgaria). We report the topographical analysis over central, parietal and occipital

electrodes (when available) in healthy and clinical datasets in Supplementary Tables 1 and 6 of Supplementary Material 2, respectively, showing comparable results.

Characteristic	Dataset 1 (A)	Dataset 2 (B)	Dataset 3 (C)	Dataset 4	Dataset 5	Dataset 6 (pediatric)
Reference to original study	Rosenblum et al., 2023 a			Jafarzadeh Esfahani et al., 2023	Rosenblum et al., 2023 b	Furrer et al., 2019; Volk et al., 2019; Jaramillo et al., 2020
No. healthy participants (-excluded)	40 (-2)	40 (-1)	33 (-1)	36 (-2)	68 (-6)	21 (0)
Exclusion reasons	>25% WASO <150-min recording	<150-min recording	>25% WASO	>25% WASO No REM	>25% WASO No REM	—
No. MDD patients (none excluded)	40	38	33	0	0	0
Study environment	Sleep lab + a memory task before[1]	Sleep lab + memory tasks before[1, 2]	Sleep lab	Home + simultaneous wearable EEG headband	Sleep lab + simultaneous blood measurement[3]	Sleep lab + MRI before and after sleep[4]
Device	Comlab 32 Digital Sleep Lab, Brainlab V 3.3 Software,	JE-209A amplifier (Nihon Kohden, Tokyo, Japan),	Comlab 32 Digital Sleep Lab, Brainlab V 3.3 Software,	Somnomedics GmbH, Randersacker, Germany	Comlab 32 Digital Sleep Lab, Brainlab V 3.3 Software,	Sensor Net for long-term monitoring (Electrical

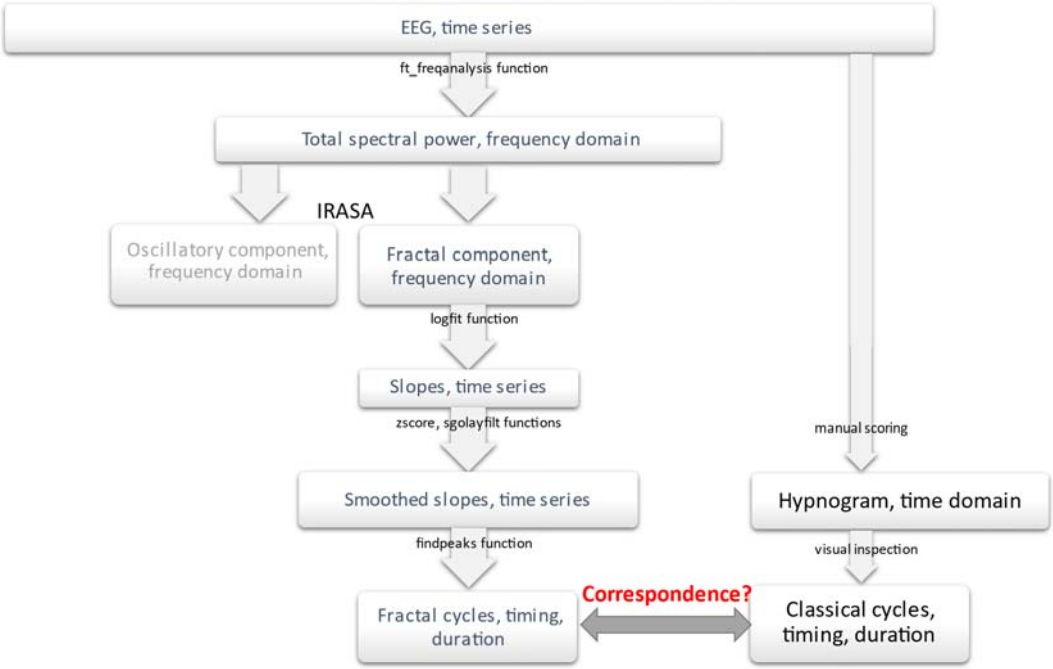
	Schwarzer, GmbH, Munich, Germany	with 128ch BrainCap (EasyCap GmbH, Herrsching, Germany)	Schwarzer GmbH, Munich, Germany		Schwarzer GmbH, Munich, Germany	Geodesic Inc., EGI, Eugene, OR, USA)
No. channels	4	128	32	24	16	128
(Offline re)-referenced to	Contralateral mastoid	Average of all leads	Average of all leads	Contralateral mastoid	Contralateral mastoid	Contralateral mastoid
Sample rate, Hz	250	200	250	256	250	500
Filtering during recording, Hz	0.3 – 70	> 0.016	0.53 – 70	0.2 – 35	0.3 – 70	0.01 – 200
Available frontal electrodes	none	Fz, F1, F2, F3, F4, F5, F6, F7, F8, F9, F10	Fz, F3, F4, F7, F8	F3, F4	F3, F4	F3, F4
Analyzed electrodes	C3, C4	F3, F4	F3, F4	F3, F4	F3, F4	F3, F4

[1] – a procedural memory paradigm (finger tapping task) before sleep, [2] – a declarative memory paradigm (word-pair learning task) before sleep, [3] – in this study, 4 ml blood were drawn every 20 minutes from the adjacent room, using an intravenous cannula and a tube extension, [4] – an MRI scan was taken in the evening before and in the morning after the sleep measurement, WASO – wake after sleep onset, REM – rapid eye movement sleep, MDD – major depressive disorder.

Fractal power component

Offline EEG data analyses were carried out with MATLAB (version R2021b, The MathWorks, Inc., Natick, MA), using the Fieldtrip toolbox and custom-made scripts. For each participant, we averaged the EEG signal over the F3 and F4 electrodes (or C3 and C4 – for Dataset 1 where the frontal channels were unavailable), calculated its spectral power for every 30 (adult datasets) or 20 (the pediatric dataset) seconds corresponding to the conventionally defined duration of sleep epochs and differentiated the total power to its fractal (i.e., aperiodic, 1/f, scale-free) and oscillatory components. Several methods to calculate fractal components exist. We opted to use the Irregularly Resampled Auto-Spectral Analysis (IRASA; Wen & Liu, 2016) tool embedded in the Fieldtrip toolbox (Oostenveld et al. 2011), one of the leading open-source EEG softwares, with the *ft_freqanalysis* function as described elsewhere (Rosenblum et al., 2022; 2023 a). A side note: slopes calculated with the IRASA strongly correlate (r = |0.9|) with those calculated using the "fitting oscillations and one over f" (FOOOF, See Supplementary Material in Schneider et al., 2022), another useful method used for aperiodic analysis (Donoghue et al., 2020). The fractal power component (shown in Fig.S1 of Supplemental Material 2) was transformed to log-log coordinates and its slope was calculated to estimate the power-law exponent (the rate of spectral decay), using the function *logfit* (Lansey, 2020). The analysis flowchart is depicted in Fig.1A; outputs of some of the analysis steps in an example individual are shown in Fig.1B.

A


EEG, time series
ft_freqanalysis function
Total spectral power, frequency domain
IRASA
Oscillatory component, frequency domain
Fractal component, frequency domain
logfit function
Slopes, time series
zscore, sgolayfilt functions
Smoothed slopes, time series
findpeaks function
Fractal cycles, timing, duration
Correspondence?
manual scoring
Hypnogram, time domain
visual inspection
Classical cycles, timing, duration

B

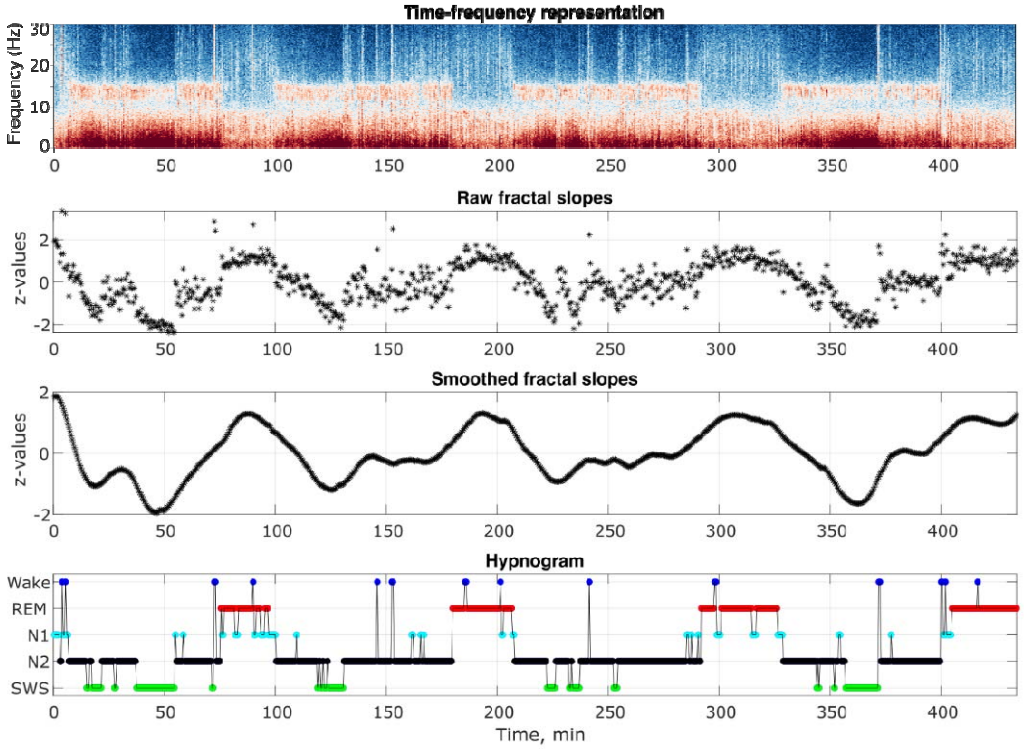

Time-frequency representation
Frequency (Hz)
Raw fractal slopes
z-values
Smoothed fractal slopes
z-values
Hypnogram
Wake
REM
N1
N2
SWS
Time, min

Figure 1. Analysis. A. Analysis flowchart. IRASA – Irregularly Resampled Auto-Spectral Analysis, *sgolayfilt* – Savitzky-Golay filter. **B.** Outputs of some of the analysis steps in an example healthy 26-year-old individual. From top to bottom: time-frequency representation of the total spectral power, raw and smoothed time series of the fractal slopes and hypnogram. Frontal spectral power and its slopes were calculated in the 0.3 – 30 Hz range for each 30 seconds of sleep.

As opposed to the oscillatory component, the fractal component is usually treated as a unity and, therefore, is filtered in the broadband frequency range (Donoghue et al., 2020; Bódizs et al., 2021; Gerster et al., 2022). Nevertheless, different studies defined (slightly) differing bands, e.g., 30 – 50Hz (Gao et al., 2017; Lendner et al., 2020), 3 – 55Hz (Waschke et al., 2021), 0.5 – 35Hz (Miskovic et al., 2019), 1 – 40Hz, 1 – 20Hz and 20 – 40Hz (Colombo et al., 2019), 1 – 45Hz (Helson et al., 2023), 0.5 – 40Hz (Vinding et al., 2023), 3 – 45Hz and 30 – 45Hz (Höhn et al., 2022) and 2 – 48Hz (Bódizs et al., 2021; Schneider et al., 2022).

Here, we used the 0.3 – 30Hz range as this is a typical sleep frequency band used in many areas of sleep research, showing good ability to differentiate between sleep stage as could be seen in Fig.S2 (Supplementary Material 2), which replicates existing literature. Dataset 4 was analyzed in the 0.3 – 18Hz range since relatively low low-pass filtering was applied to it during the recording (see Table 1). In Supplementary Table 2 (Supplementary Material 2), we also analyze the 1 – 30Hz band to control for a possible distortion (the so called “knees'' of the spectrum) of the linear fit by excluding low frequencies with strong oscillatory activity (Gao et al., 2017; Bódizs et al., 2021). We find that the results are similar to those obtained for the 0.3 – 30Hz band reported in the Main text (probably thanks to the smoothening procedure we applied).
Finally, Fig.S3 (Supplementary Material 2) shows aperiodic slopes in the 30 – 48Hz band averaged over sleep stages for Datasets 1 – 3 and 5. According to literature, REM sleep is expected to show the steepest (most negative) high-band slopes compared to all other sleep stages. However, we were able to replicate this finding in Datasets 1 and 5 only. Given poor differentiation between the stages in 2/4 datasets, this variable was not used in any further analyses.

Fractal cycles

Time series of the fractal slopes were z-normalized (raw values can be seen in Fig.S2 (Supplementary Material 2) within a participant and smoothened with the Savitzky-Golay filter (Fig.1), the filter highly used in many fields of data processing. We used the Matlab's function *sgolayfilt(slope_time_series, order, frame_length)* with the polynomial order of five and the frame length of 101. The peaks of the smoothed time series of the fractal slopes were defined with Matlab's function *findpeaks (slope_time_series, 'MinPeakDistance', 40, 'MinPeakProminence', 0.9)* with the minimum peak distance of 20 minutes (i.e., forty 30-second epochs) and minimum peak prominence of |0.9| z (Fig. 2). The amplitude of the descending and ascending phases of a cycle was defined to be > |0.9| z, meaning that there is a probability of p=0.8 that a given fractal slope lies below/above the standard normal distribution.

Of note, we had no solid *a priori* theoretical indication for choosing either of the function settings mentioned above. All settings were chosen *a posteriori* following an exploratory visual inspection of the normalized data from one dataset (Dataset 5), which therefore can be transferred to other datasets. That is, in datasets 1 – 4 and 6, the settings of the *sgolayfilt* and *findpeaks* functions were defined *a priori* based on the results obtained while inspecting Dataset 5.

Classical sleep cycles

Classical sleep cycles were defined manually via the visual inspection of the hypnograms according to the criteria originally proposed by Feinberg and Floyd (1979) with some adaptations as follows. A cycle typically starts with N1, N2 or sometimes wake and is followed by N2 or N2 and slow-wave sleep (SWS) > 20 minutes in duration, which can include wake. The cycle ends with the end of the REM period, which can include wake or short segments of non-REM sleep. No minimum REM duration criterion was applied (Tarokh et al., 2012). In some cases (described below), the cycle end was defined at a non-REM sleep stage or wake. Three examples of typical hypnograms with marked classical sleep cycles are shown in Fig.2.

Given the absence of strict and broadly accepted rules for cycles with skipped REM sleep definition in literature, here, we tagged a cycle as "skipped" based on the visual inspection of the hypnogram combined with the criteria proposed by Jenni and Carskadon (2004) and Tarokh et al. (2012). Specifically, we subdivided a long cycle > 110 minutes into two when: 1) there was a "lightening of sleep" (i.e., the presence of wake, N1 and N2) in the middle of the long cycle, when a REM sleep episode was anticipated, 2) a continuous episode of N1, N2, wake or movement time lasting at least 12 minutes was preceded and followed by slow-wave sleep (Jenni & Carskadon, 2004); 3) two clear episodes of slow-wave sleep were separated by lighter non-REM stages (which might include wake) (Campbell et al., 2011; Tarokh et al., 2012). Long cycles containing skipped cycles were divided into cycles at time of sleep lightening. Examples of hypnograms with skipped sleep are shown in Fig.9 and Fig.7 (S21 and S6).

The last incomplete (not terminated by the REM sleep phase) cycle at the end of the night was included in the analysis if its duration was > 50 minutes. The last incomplete cycles < 50 minutes were removed (nevertheless, they are shown in figures when present).

Statistical analysis

The assumption that durations of the fractal and classical cycles come from a standard normal distribution was tested using the one-sample Kolmogorov-Smirnov test. The result suggested that this assumption should be rejected ($p<0.05$); therefore, non-parametric tests were used for all further analyses.

We correlated fractal and classical cycle durations using Spearman's correlations in each dataset separately as well as in all datasets pooled. Given that in some participants (from 34 to 55% in different datasets), the number of the fractal cycles (mean 4.6 ± 1.0 cycles per participant) was not equal to the number of the classical cycles (mean 4.7 ± 0.9 cycles per participant), prior to the correlation analysis, we averaged the duration of the fractal and classical cycles over each participant. For a subset of the participants (45 – 66% of the participants in different datasets) with a one-to-one match between the fractal and classical

cycles, we performed an additional correlation without averaging, i.e., we correlated the durations of individual fractal and classical cycles.

In addition, we computed person-centered effect sizes, the approach that answers the question, "How many participants in the study showed the consistent with theoretical expectation effect?". This approach helps to reveal data patterns that are missed by traditional statistical analyses (Grice et al., 2020). We calculated the sample prevalence by counting the number of significant correlations between fractal and classical cycle duration divided by the total number of cases (both significant and non-significant).

To assess the population prevalence of the findings with associated uncertainty, we used the Bayesian prevalence, accounting for the false positive rate of the statistical test (Ince et al., 2022). This method helps to estimate the proportion of the population that would show the effect if they were tested in this experiment or, in other words, the population within-participant replication probability (Ince et al., 2022). As an output, this method provides the maximum *a posterior* estimate – the most likely value of the population parameter. To quantify the uncertainty of this estimate, Bayesian prevalence also provides the highest posterior density intervals for various levels (we used the 96% probability level) – the range within which the true population value lies with the specified probability. To perform this analysis we used an online web application available at https://estimate.prevalence.online.

To compare pediatric and young adult groups (Supplementary Table 3, Supplementary Material 2), MDD patients and controls (Table 3), MDD patients treated with REM-suppressive antidepressants and patients treated with REM-non-suppressive antidepressants (Supplementary Table 5 in Supplementary Material 2), we used the non-parametric Mann-Whitney U test. We performed the analyses both at the cycle level (while pooling the cycles of all participants together) as well as at the subject level (while averaging the cycles of a given participant). Given that the results of both analyses were similar, we report only the cycle level analysis for simplicity. To compare medicated and unmedicated states of the MDD patients (Table 3), we used the paired samples Wilcoxon test. Effect sizes were calculated with Cohen's d.

In Supplementary Material 2, we report autocorrelations and partial autocorrelations of fractal slope time series (Fig.S6) as well as cross-correlations (Fig.S7) between time series of fractal slopes vs. time series of non-REM or REM sleep proportion to further model their temporal relationships.

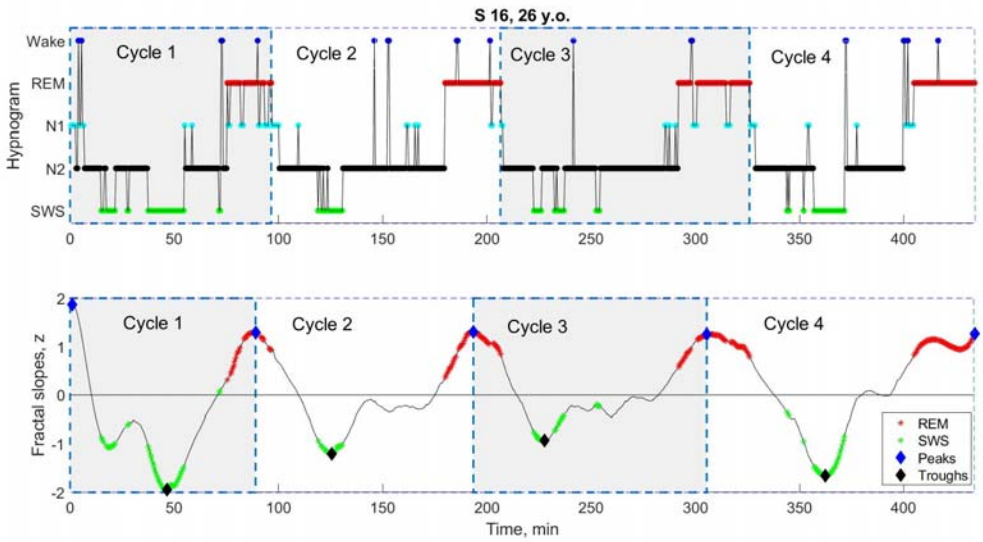
Data and code sharing

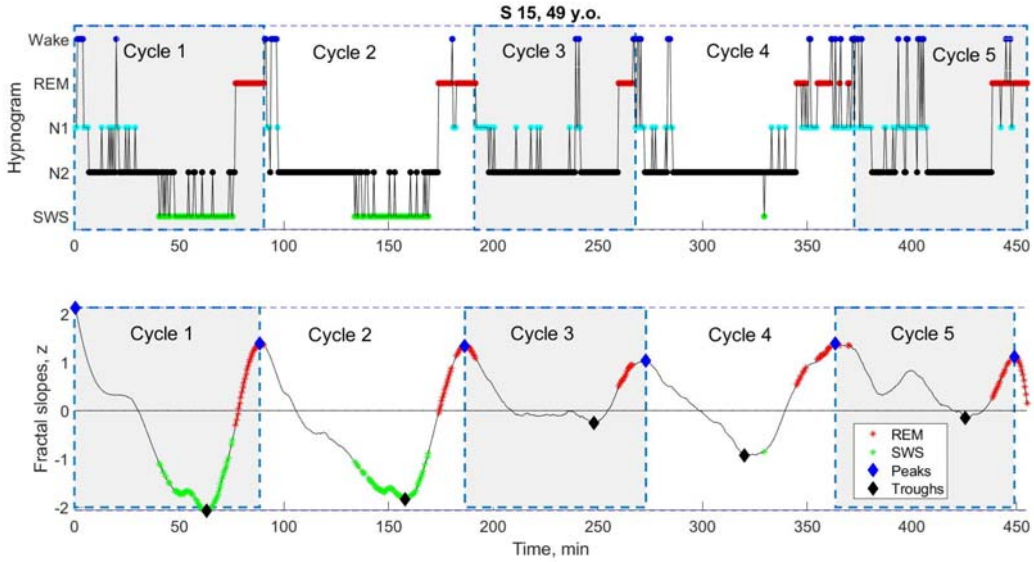
The fractal slope and sleep stage for each 30-second epoch of sleep for each healthy adult participant, Matlab scripts calculating fractal slopes and fractal cycles and Excel file used to perform all the statistical analyses with the fractal and sleep characteristics for each participant can be accessed under https://osf.io/gxzyd.

Results

Fractal cycles in healthy adults

We observed that the slopes of the fractal (aperiodic) power component fluctuate across a night such that the peaks of the time series largely coincide with REM sleep episodes while the troughs of the time series for the most part coincide with non-REM sleep episodes. Fig.2 displays smoothed fractal slope time series and hypnogram for three example subjects. The rest of the participants are reported in Supplementary Material 1.


S 16, 26 y.o.
Hypnogram
Wake
REM
N1
N2
SWS
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Fractal slopes, z
REM
SWS
Peaks
Troughs
Time, min


S 15, 49 y.o.
Hypnogram
Wake
REM
N1
N2
SWS
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Fractal slopes, z
REM
SWS
Peaks
Troughs
Time, min

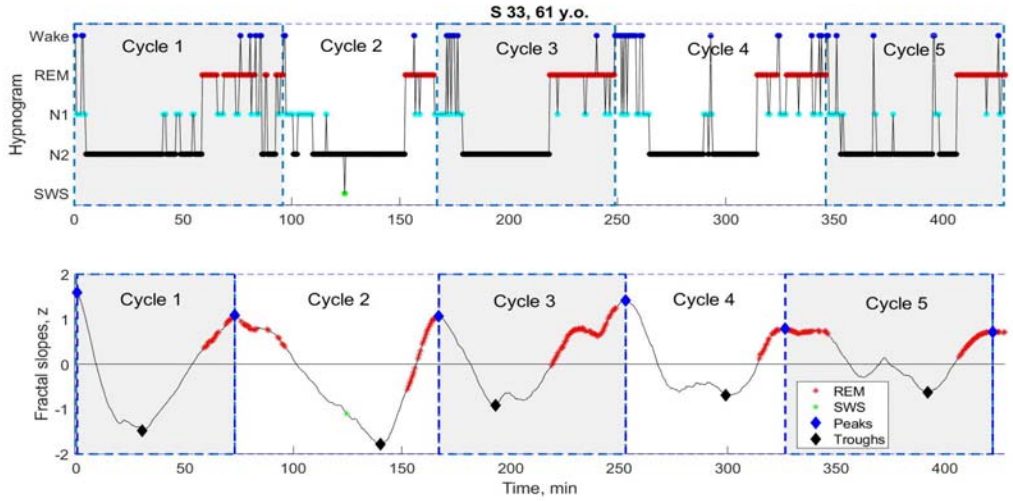

S 33, 61 y.o.
Hypnogram
Wake
REM
N1
N2
SWS
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Fractal slopes, z
REM
SWS
Peaks
Troughs
Time, min

Figure 2. Individual fractal and classical sleep cycles: one-to-one match. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top) observed in three participants of different ages (from Dataset 3). The duration of the fractal cycle is a time interval between two successive peaks (blue diamonds). There is a one-to-one match between fractal cycles defined by the algorithm and classical (non-REM – REM) cycles defined by the hypnogram. Time series of the fractal slopes and corresponding hypnograms for all participants are reported in Supplementary Material 1. SWS – slow-wave sleep, REM – rapid eye movement.

Based on this observation we propose the following definition of the "fractal cycle" of sleep:

Definition: The fractal cycle of sleep is a time interval during which the time series of the fractal slopes descend from the local maximum to the local minimum with the amplitudes higher than |0.9| z, and then lead back from that local minimum to the next local maximum.

Then, we created an algorithm, which automatically defined the onset and offset of the fractal cycles (the adjacent peaks of the time series of the fractal slopes) (https://osf.io/gxzyd/). We visually inspected the output of the algorithm and found that the automatic definition (Fig.2, blue diamonds) was identical to that provided by a human scorer.

Further visual inspection revealed that fractal slopes cyclically descend and ascend 4 – 6 times per night and the average duration of such a descent-ascent cycle is close to 90 minutes. Fig.3 (upper panel) shows the frequency distribution of the fractal cycle durations for each dataset separately as well as for the pooled dataset.

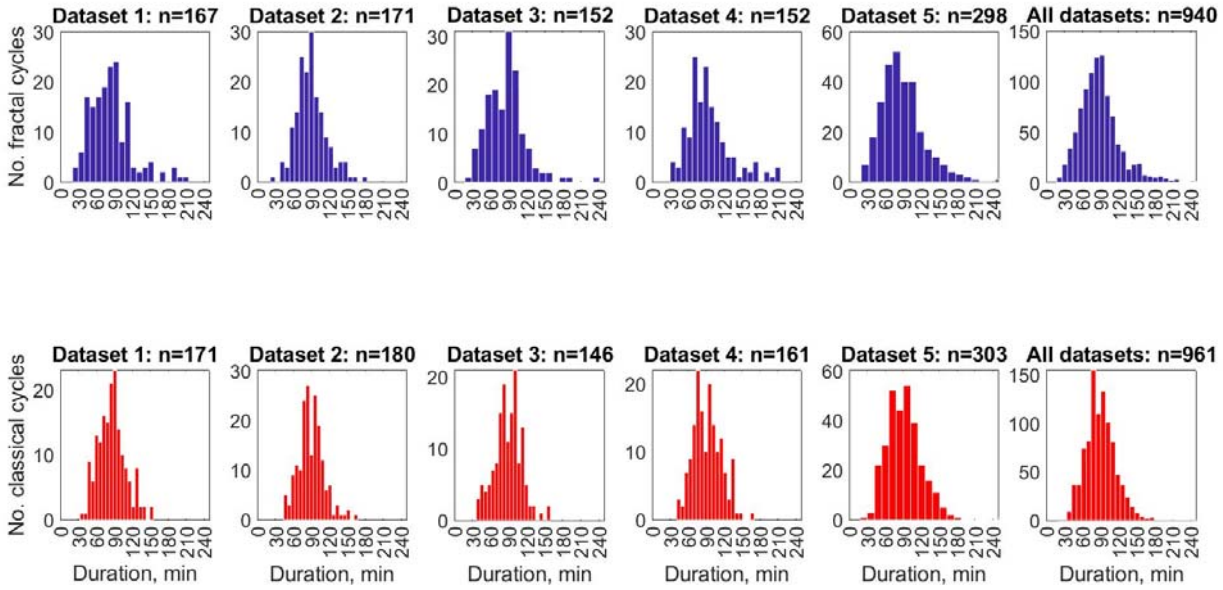
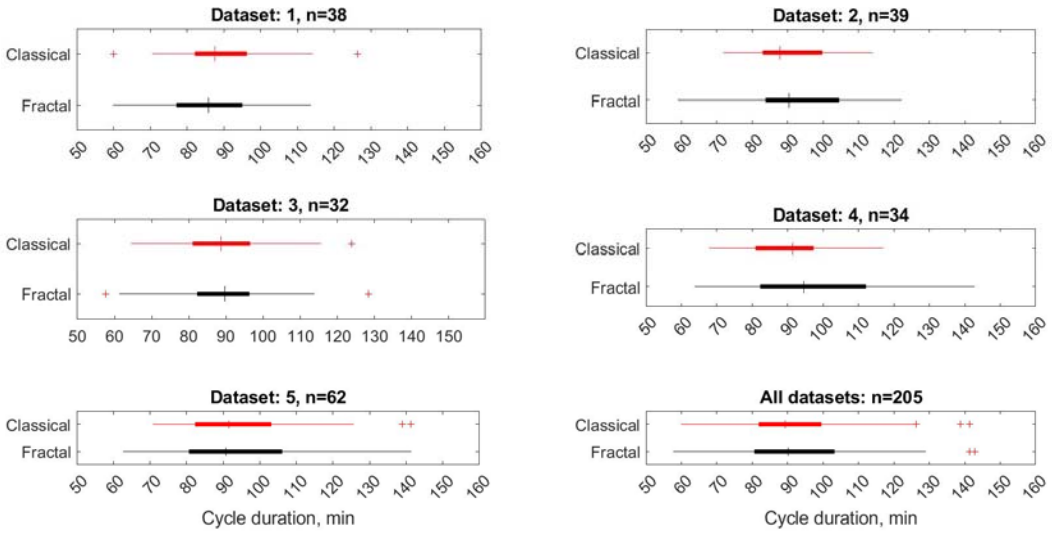


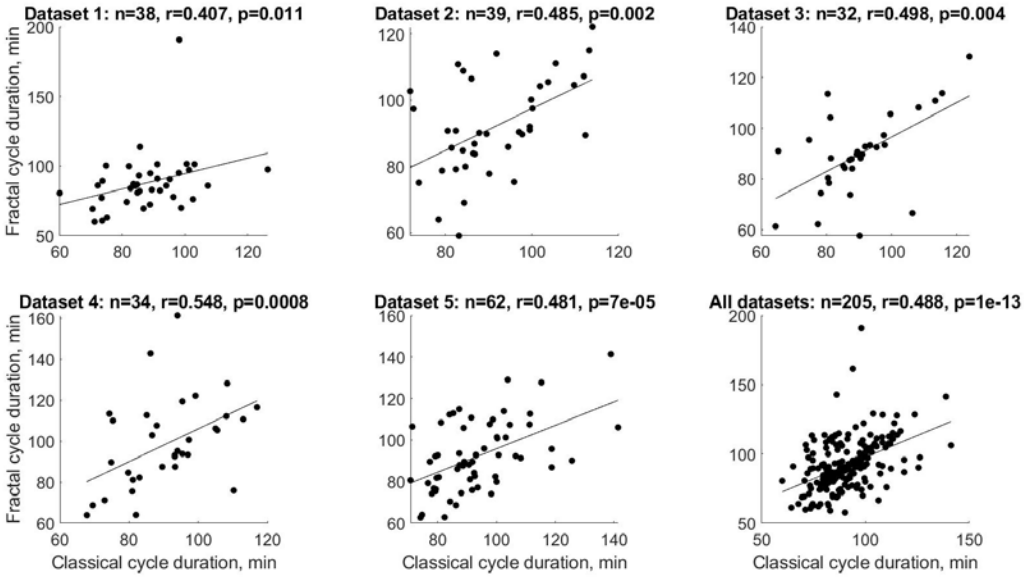
Figure 3. Frequency distribution of the duration of fractal and classical cycles. The individual fractal (top) and classical (bottom) cycles are counted (n) for each dataset separately and for all datasets merged. Across studies, 205 healthy adult participants provided 940 fractal cycles with a mean of 4.6 ± 1.0 cycles per participant and 961 classical cycles with a mean of 4.7 ± 0.9 cycles per participant. For both fractal and classical cycles, Kolmogorov-Smirnov test rejected the assumption that cycle duration comes from a standard normal distribution.

This observation strikingly resembles what we know about classical sleep cycles: "night sleep consists of 4 – 6 sleep cycles, which last for about 90 minutes each" (Feinberg & Floid, 1979; Le Bon, 2020; Fig. 3, bottom panel). Further calculations showed that the mean duration of the fractal cycles averaged over all cycles from all datasets (n = 940) is 89 ± 34 minutes while the mean duration of the classical sleep cycles is 90 ± 25 minutes (Fig. 4A). The mean durations of the fractal and classical sleep cycles averaged over each participant correlated in all analyzed datasets (r = 0.4 – 0.5, Table 2, Fig. 4B).

A


Dataset: 1, n=38
Dataset: 2, n=39
Dataset: 3, n=32
Dataset: 4, n=34
Dataset: 5, n=62
All datasets: n=205
Classical
Fractal
Cycle duration, min

B


Dataset 1: n=38, r=0.407, p=0.011
Dataset 2: n=39, r=0.485, p=0.002
Dataset 3: n=32, r=0.498, p=0.004
Dataset 4: n=34, r=0.548, p=0.0008
Dataset 5: n=62, r=0.481, p=7e-05
All datasets: n=205, r=0.488, p=1e-13
Fractal cycle duration, min
Classical cycle duration, min

C

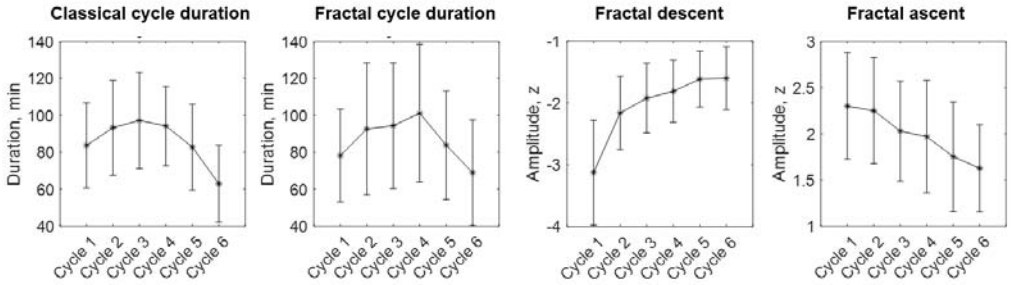

Classical cycle duration
Fractal cycle duration
Fractal descent
Fractal ascent
Duration, min
Amplitude, z
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

Figure 4. Fractal and classical sleep cycle duration. A. Box plots: in each box, a vertical central line represents the median, the left and right edges of the box indicate the 25th and 75th percentiles, respectively, the whiskers extend to the most extreme data points not considered outliers, and a plus sign represents outliers. **B.** Scatterplots: each dot represents the duration of the cycles averaged over one participant. The durations of the fractal and classical sleep cycles averaged over each participant correlate in all analyzed datasets, raw (non-ranked) values are shown, r – Spearman's correlation coefficient. **C.** Cycle-to-cycle overnight dynamics show an inverted U shape of the duration of both fractal and classical cycles across a night and a gradual decrease in absolute amplitudes of the fractal descents and ascents from early to late cycles.

Characteristic	**Dataset 1**	**Dataset 2**	**Dataset 3**	**Dataset 4**	**Dataset 5**	**Pooled dataset**
No. participants analyzed	38	39	32	34	62	301
Age, years	46.8 ± 10.7	31.0 ± 9.9	45.3 ± 15.9	21.5 ± 3.8	37.4 ± 15.3	36.7 ± 15.0
Age range, years	29 – 65	19 – 54	22 – 75	18 – 35	20 – 66	18 – 75
Gender, female, %	53	54	61	68	55	58
Wake, %	6.0	4.9	7.5	7.1	9.1	7.0
Non-REM stage 1, %	7.7	11.9	9.0	3.6	7.5	7.9
Non-REM stage 2, %	48.1	45.9	49.3	34.7	46.1	45.1
Slow-wave sleep, %	19.2	20.3	16.2	34.2	17.2	20.9

REM sleep, %	19.0	16.9	17.9	19.3	19.3	18.6
Total sleep time, min	394 ± 55	430 ± 26	434 ± 37	445 ± 62	467 ± 38	438 ± 51
Classical sleep cycle duration, min	86.2 ± 23.3	90.0 ± 21.3	89.0 ± 22.7	92.2 ± 23.7	91.9 ± 29.0	90.1 ± 24.9
Fractal sleep cycle duration, min	86.4 ± 35.2	90.0 ± 25.5	86.4 ± 31.2	94.7 ± 37.1	89.9 ± 37.1	89.1 ± 34.0
Classical-fractal cycles duration correlation, r	0.407	0.485	0.498	0.548	0.481	0.488
Classical-fractal cycles duration correlation, p	0.011	0.002	0.004	0.001	10^{-5}	10^{-13}
One-to-one match between classical and fractal cycles timing and duration, % cycles	78	88	82	87	77	81
Participants having all fractal and classical cycles in a one-to-	53	62	66	53	45	54

one match, % participants						
Descent amplitude, z	-2.2 ± 0.9	-2.3 ± 0.9	-2.2 ± 0.8	-2.2 ± 0.8	-2.1 ± 0.8	-2.2 ± 0.8
Ascent amplitude, z	2.1 ± 0.6	2.2 ± 0.6	2.1 ± 0.6	2.1 ± 0.6	2.0 ± 0.6	2.2 ± 0.6
No. fractal cycles	167	171	152	152	298	940
No. classical cycles	171	180	146	161	303	961
No. "skipped" first cycles (%)	4 (11%)	7 (18%)	0	19 (56%)	15 (24%)	45 (22%)

± shows mean and SD, r – Spearman's correlation coefficient, "skipped" cycle – a cycle where the REM phase is expected to appear except that it does not, REM – rapid eye movement, HC – healthy controls.

Further analysis at the individual level revealed that 81% (763/940) of all fractal cycles (77 – 88% in different datasets) could be matched to a specific classical cycle defined by hypnogram, i.e., the timings of fractal and classical cycles approximately coincide. Bayesian prevalence analysis further revealed that the Bayesian highest posterior density interval with 96% probability level lies within the 0.77 – 0.83 range (the range within which the true population value lies) and the maximum *a posteriori* point estimate prevalence is equal to 0.8, reflecting the most likely values for the population parameter. This analysis reflects the within-participant replication probability: the probability of obtaining a significant experimental result if the same experiment was applied to a new participant randomly selected from the population (Ince et al., 2022).

The timings and correlations between the fractal and classical cycles were not perfect (r = 0.6 – 0.8, p<0.001) as our algorithm defines the end of a cycle when fractal activity reaches a local maximum and not at the end of the REM episodes as requires the definition of a classical cycle. In some cases, the match between fractal and classical cycles was rather coarse-grained (See, for example, cycle 3 in S16, Figure 2). This could be explained by the fact that sometimes, especially towards morning, REM periods are rather long.

In 54% (111/205) of the participants (45 – 66% in different datasets), all fractal cycles approximately coincided with classical cycles (r = 0.5 – 0.8, p < 0.001, Fig.5, Table 2). Bayesian prevalence analysis revealed that the maximum *a posteriori* point estimate prevalence is equal to 0.52 and the Bayesian highest posterior density interval (the true population level) with 96% probability level lies within the 0.45 – 0.60 range.

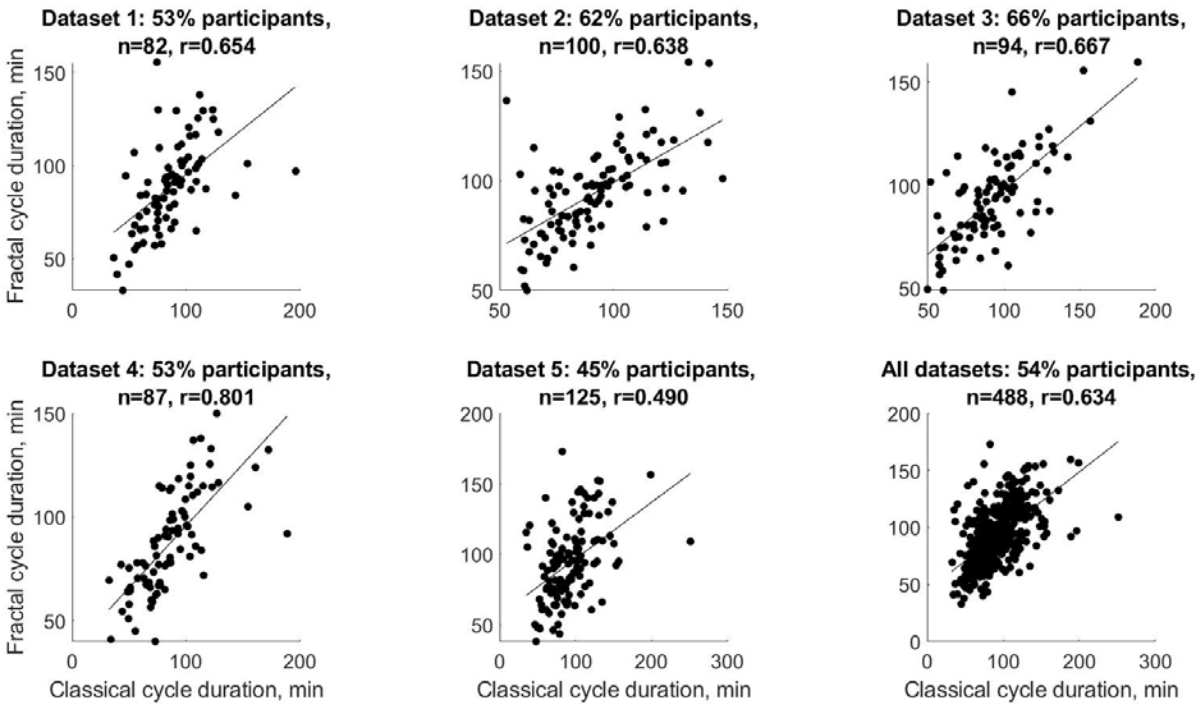
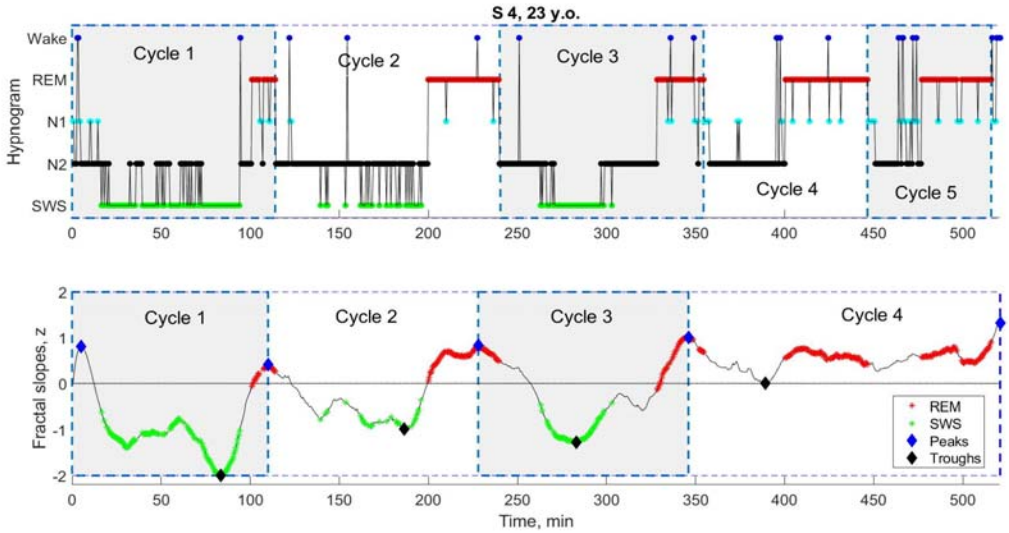


Figure 5. A subset: a one-to-one match between fractal and classical sleep cycles. In a subset of the participants (from 45 to 66% in different datasets), there was a one-to-one match between fractal and classical cycles, each dot represents an individual cycle, n – number of cycles, all p-values < , r – Spearman's correlation coefficient.

In the remaining participants, some – but not all – fractal cycles could be matched to a specific classical cycle. Fig.6 displays examples of some mismatch between classical and fractal cycles in three different participants. More examples can be found in Supplementary Material 1. We noticed that there were more fractal cycles in cases where the proportion of wake after sleep onset was relatively high since our algorithm defined both REM- and wake-related smoothed fractal slopes as local peaks (Fig.6, S22). We hypothesized that this fact had led to a mismatch between the number of classical and fractal cycles and, therefore, performed an additional control analysis. Namely, we defined fractal cycles using a time series where all wake-related slopes were replaced with NaNs (Not-a-Number). Intriguingly, this procedure did not change the strength of correlations between fractal and classical cycle durations (r = 0.46 for NaNs-time series vs r = 0.49 for original time series, both p-values < 0.001, n = 205).



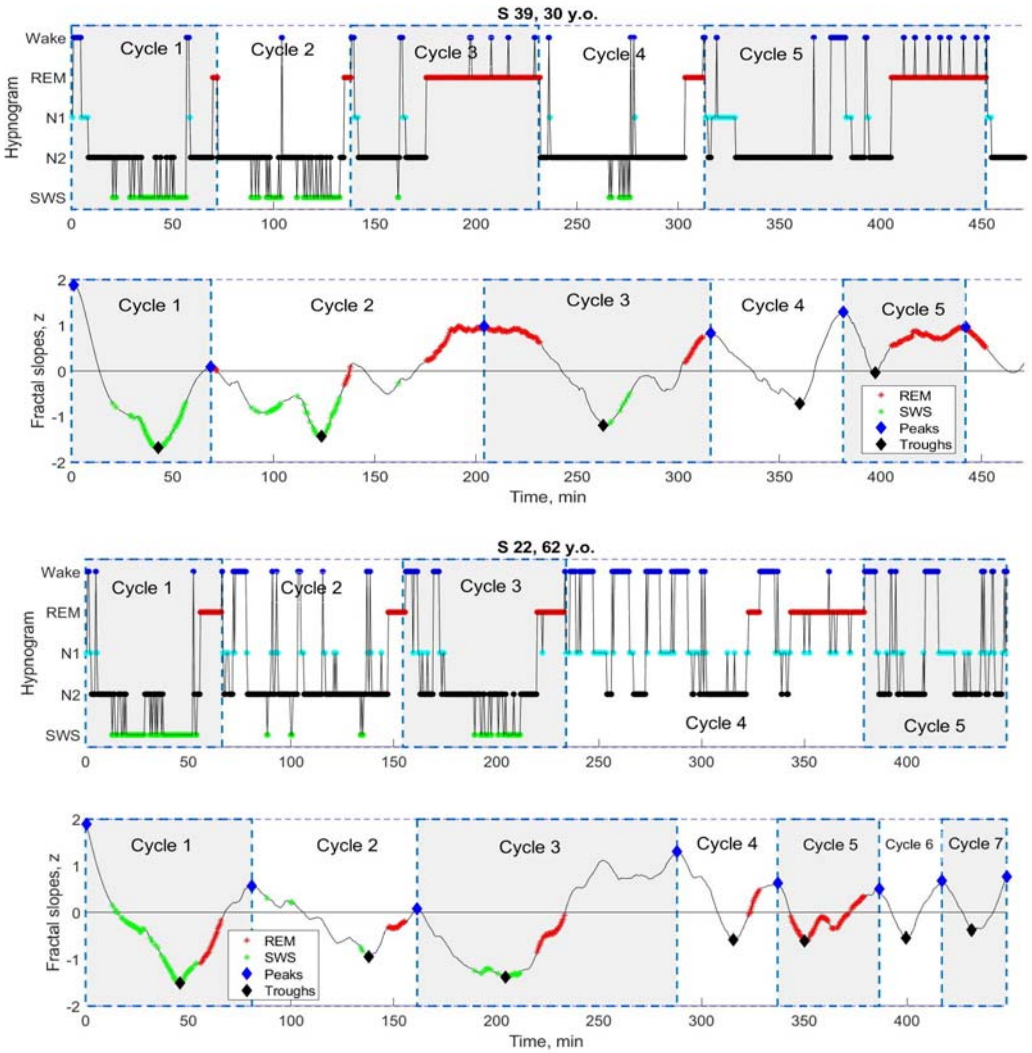

S 39, 30 y.o.
Wake
REM
N1
N2
SWS
Hypnogram
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Fractal slopes, z
REM
SWS
Peaks
Troughs
Time, min
S 22, 62 y.o.
Cycle 6
Cycle 7

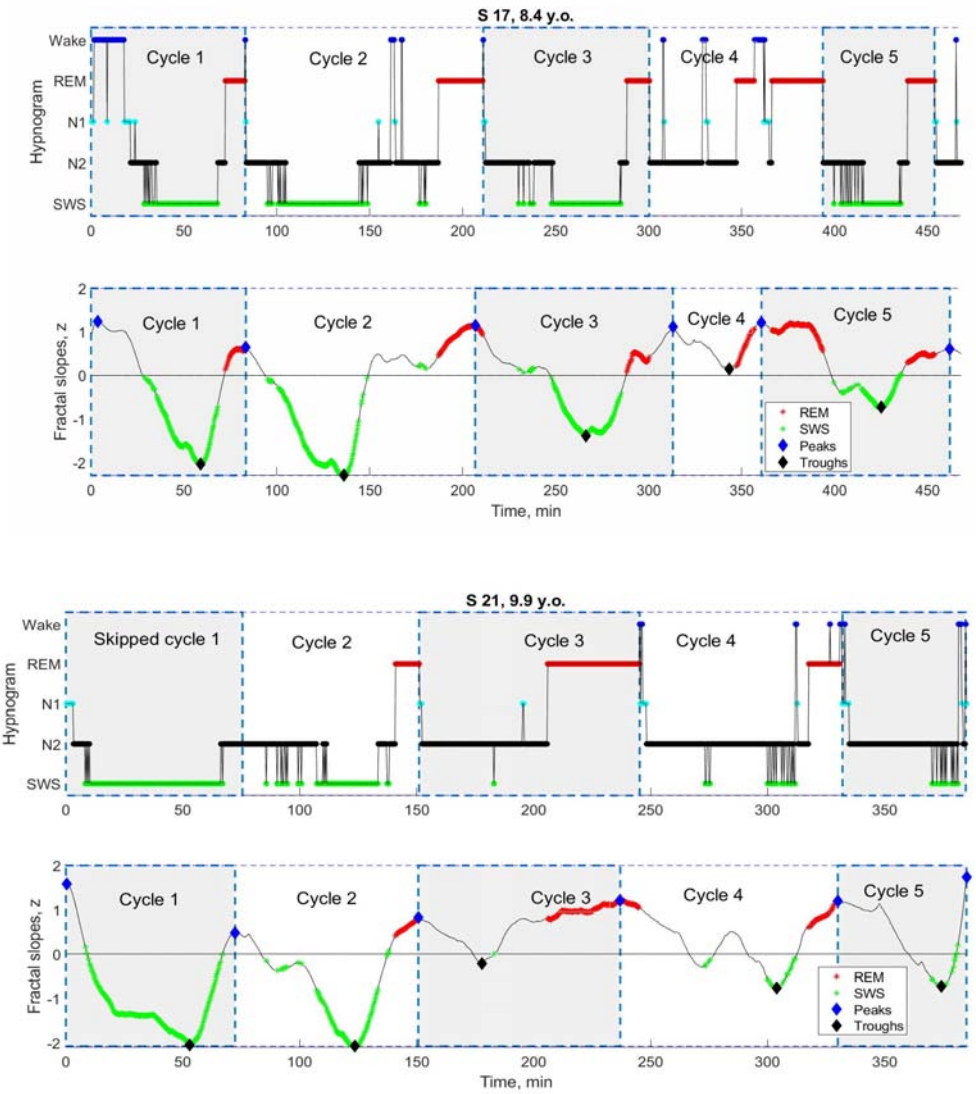
Figure 6. Individual fractal and classical sleep cycles: algorithm's misses. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top) observed in three participants of different ages (from Dataset 5). The duration of the fractal cycle is an interval of time between two successive peaks (blue diamonds) defined with the Matlab function *findpeaks* with the minimum peak distance of 40 minutes and minimum peak prominence of 0.9 z. In S4, the fourth fractal cycle corresponds to two classical cycles, No.4 and No.5, since the algorithm misses the local fractal peak at the 410th minute, which is not high enough (< |0.9| z). In S39, the second fractal cycle corresponds to two classical cycles, No.2 and No.3: the algorithm misses the local fractal peak at the 140th minute (the time of the corresponding REM episode), as the amplitude of the subsequent fractal descent is < |0.9| z. Two fractal cycles, No. 4 and No. 5, correspond to one classical cycle, No. 5: the algorithm identifies the wake episode at the 380th minute (in the middle of the 5th classical cycle) as a local fractal peak, i.e., the end of the fractal cycle. In S22, the second part of night has many wake epochs, some of them are identified by the algorithm as local peaks. This results in a higher number of fractal cycles as compared to the classical ones and a poor match between the fractal cycles No. 3 – 7 and classical cycles No. 2 – 5. The algorithm does not distinguish between the wake and REM-related fractal slopes and can define both as local peaks. Since the duration of the fractal cycles is defined as an interval of time between two adjacent peaks, more awakenings/arousals during sleep (usually associated with aging (Fig. 10 top right)) are expected to result in more peaks and, consequently, more fractal cycles, i.e., a shorter cycle duration. This is one of the possible explanations for the correlation between the fractal cycle duration and age (Fig. 10 top left). SWS – slow-wave sleep, REM – rapid eye movement.

Cycle-to-cycle overnight dynamics showed an inverted U-shape of the duration of both fractal and classical cycles and a gradual decrease in absolute amplitudes of the fractal descents and ascents from early to late cycles (Fig.4C).

Finally, Fig.S4 (Supplemental Material 2) shows fractal activity across 13-h, including 3 hours before the sleep onset and 2 hours after awakening. The pattern of fractal fluctuations suggests that fractal cycles are specific to sleep and are not observed during wake.

Fractal cycles in children and adolescents

Smoothed fractal slope time series and hypnograms for three example children are shown in Fig.7. Demographic and sleep characteristics of children and adolescents are reported in Supplementary Table 3 (Supplementary Material 2).


S 17, 8.4 y.o.
Wake
REM
N1
N2
SWS
Hypnogram
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Fractal slopes, z
REM
SWS
Peaks
Troughs
Time, min
S 21, 9.9 y.o.
Skipped cycle 1

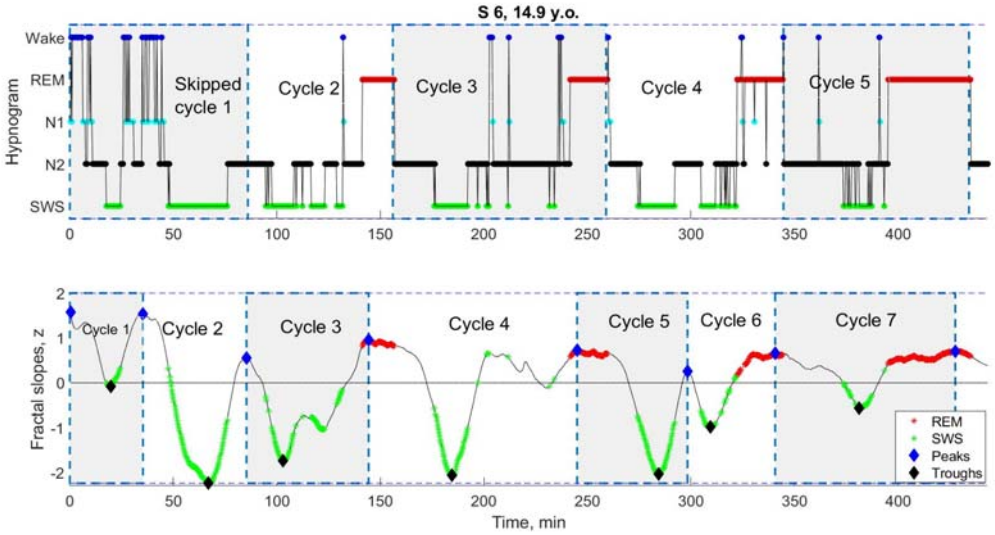
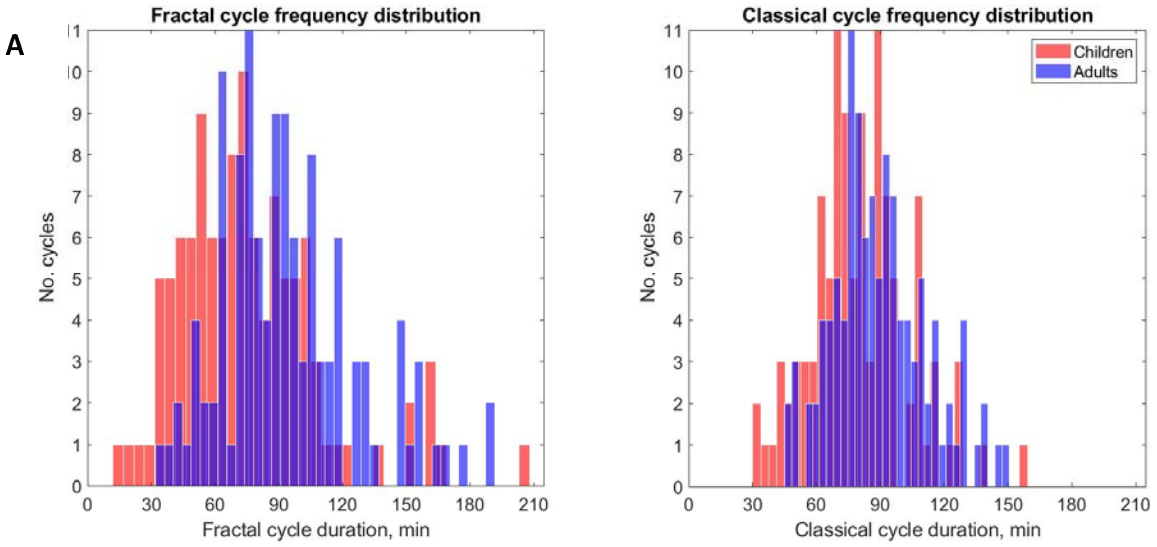


Figure 7. Individual fractal and classical sleep cycles in children and adolescents. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top) observed in three pediatric participants of different ages (Dataset 6). The duration of the fractal cycle is a time interval between two successive peaks (blue diamonds) defined with the Matlab function *findpeaks* with a minimum peak distance of 20 minutes and minimum peak prominence of 0.9 z. In S17, there is a one-to-one match between fractal and classical (non-REM – REM) cycles defined by the hypnogram. Because of a transient wake period at the 360th minute that was defined as a local peak by the fractal cycle algorithm, fractal cycle 4 is shorter than classical cycle 4. In S21, we split the first 150-minute-long classical cycle into two cycles according to the definitions of a "skipped" cycle presented in Methods. The fractal cycle algorithm successfully detected this skipped cycle. S6 has a 156-minute-long first classical cycle. Visual inspection shows that it should be divided into 3 skipped cycles, however, our *a priori* definition of skipped cycles did not include an option to subdivide a long cycle into three short cycles; hence, we split it into two short cycles. The fractal cycle algorithm was sensitive to these sleep lightenings and detected all three short cycles. Classical cycle 4 looks like a skipped cycle as it has two clear episodes of slow-wave sleep separated by non-REM stage 2. However, the length of this cycle is shorter than 110 min (the threshold defined *a priori*), therefore, we did not split the classical cycle 4 into two cycles. The fractal cycle algorithm was sensitive to this lightening of sleep and defined two fractal cycles during this period. SWS – slow-wave sleep, REM – rapid eye movement.

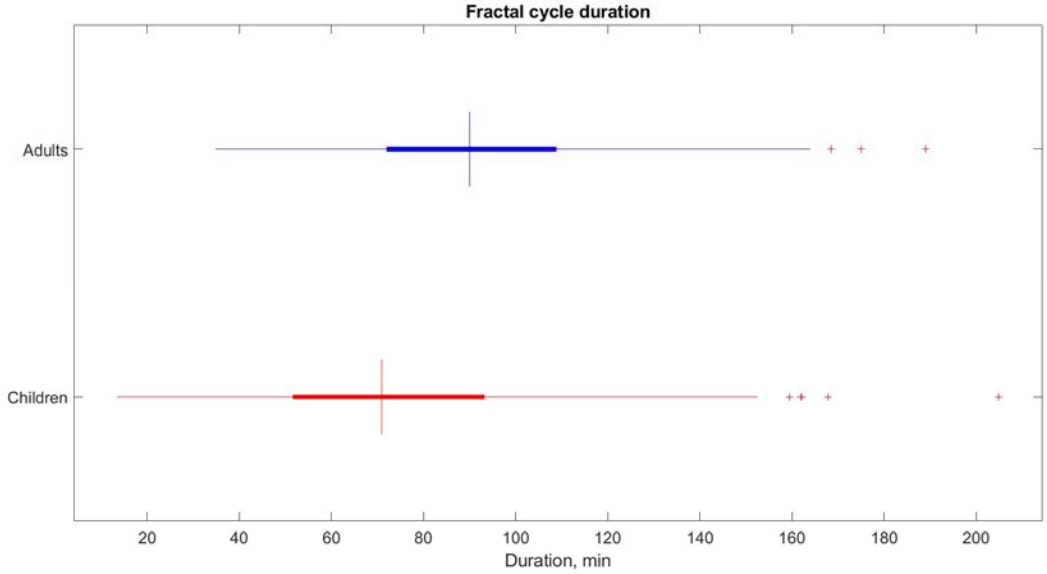
We found that children and adolescents (mean age: 12.4 ± 3.1 years, n = 21) showed a shorter duration of both fractal (76 ± 34 vs 94 ± 32 min, p<0.001, Cohen's d=-0.56, 112 vs 121 pooled cycles, 5 cycles/participant vs 4.4 cycles/participant) and classical cycles (80 ± 23 vs 90 ± 22 min,

p<0.001, Cohen's d = -0.46, 112 vs 114 pooled cycles) compared to young adults (mean age: 24.8 ± 0.9 years, n = 24) with a medium effect size (Fig.8A – B).

Cycle-to-cycle overnight dynamics further revealed that only the mean durations of the first two fractal cycles and the fourth classical cycle were significantly shorter in the pediatric compared to control group with a medium and large effect sizes, respectively (Fig.8C).



B


Fractal cycle duration
Adults
Children
20
40
60
80
100
120
140
160
180
200
Duration, min

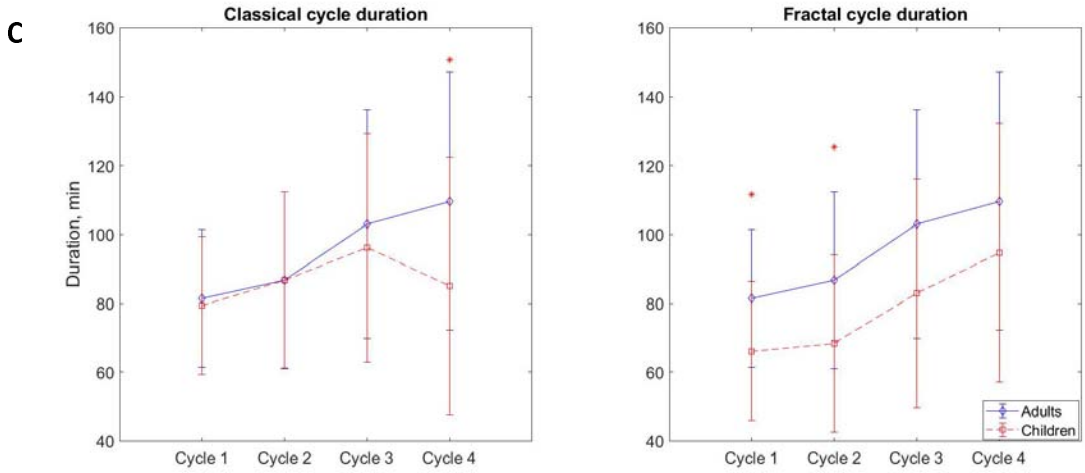


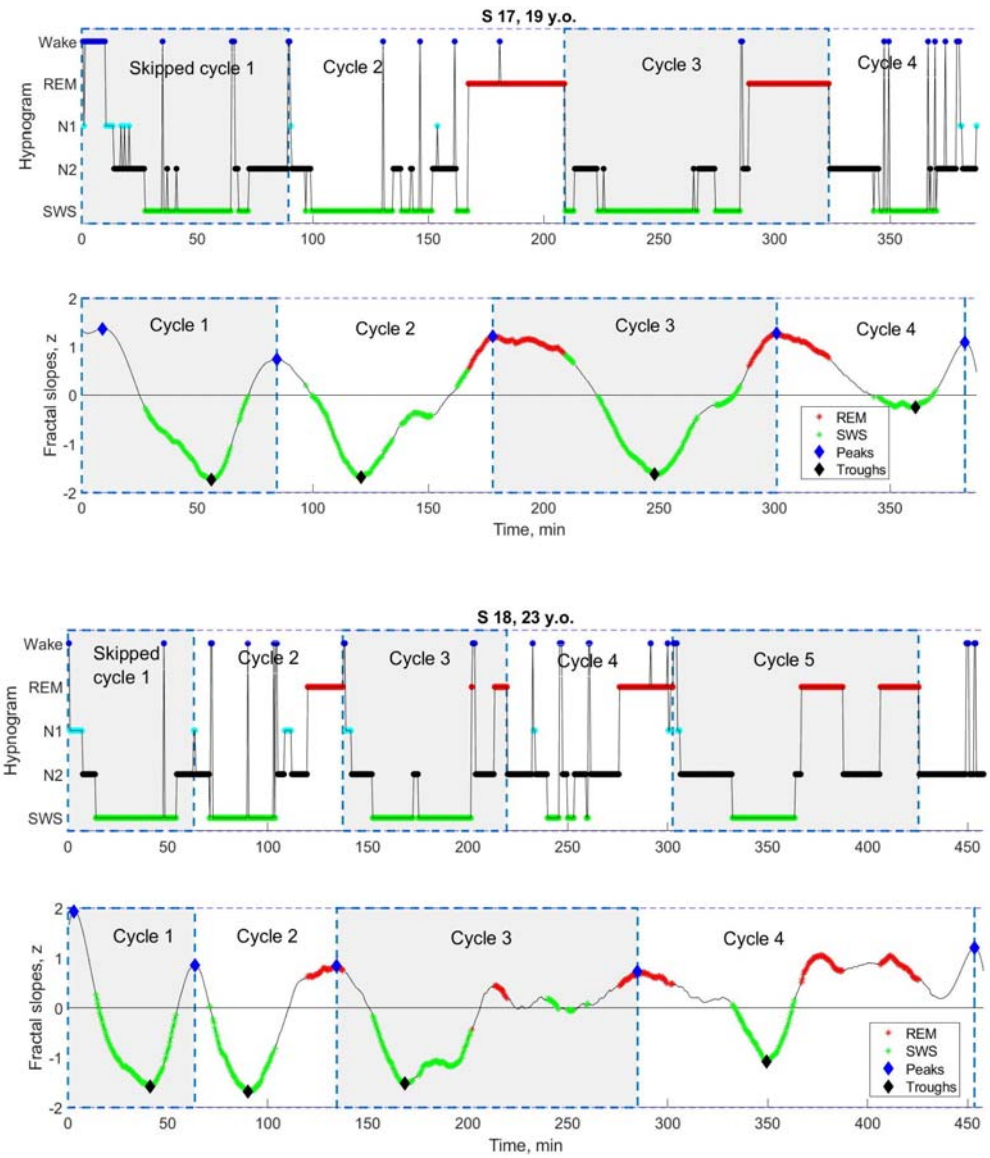
Figure 8. Fractal and classical sleep cycles in children and adolescents. A. Histograms: The frequency distribution of fractal (left) and classical (right) cycle durations in children and adolescents (mean age: 12.4 ± 3.1 years) compared to young adults (mean age: 24.8 ± 0.9 years). Kolmogorov-Smirnov's test rejected the assumption that cycle duration comes from a standard normal distribution. **B. Box plots:** in each box, a vertical central line represents the median, the left and right edges of the box indicate the 25th and 75th percentiles, respectively, the whiskers extend to the most extreme data points not considered outliers, and a plus sign represents outliers. Children and adolescents show shorter fractal cycle duration compared to young adults**. C. Overnight dynamics.** Cycle-to-cycle dynamics show that only the mean durations of the first two fractal cycles are significantly shorter in the pediatric compared to control group, * marks a statistically significant difference between the groups.

"Skipped" cycles

Overall (Datasets 1 – 6), visual inspection of the hypnogram revealed that 55 out of the 226 (24%) first sleep cycles had no REM episode (being referred to as "skipped" cycles). Specifically, in the pediatric dataset, we detected 10 "skipped" first cycles (i.e., in 48% of the tested children and adolescents, the expected-to-appear REM episodes of the first cycles were skipped). The number of the "skipped" first cycles for each one of the adult datasets is reported in Table 2. Two example "skipped" cycles in children and three example "skipped" cycles in young adults are shown in Fig.7 (S21 and S6) and Fig.9, respectively. For simplicity and between-subject

consistency, we included in the analysis only the first cycles; however, it should be noted that in some cases, “skipped” cycles were observed later in the night as well.

The fractal cycle algorithm detected “skipped” cycles in 53 out of 55 (96%) of cases with one miss in Dataset 2 and another miss in Dataset 5 (Supplementary Material 1). Bayesian prevalence analysis revealed that the maximum *a posteriori* point estimate prevalence is equal to 0.96 and the Bayesian highest posterior density interval (the true population level) with a 96% probability level lies within the 0.88 – 0.99 range.



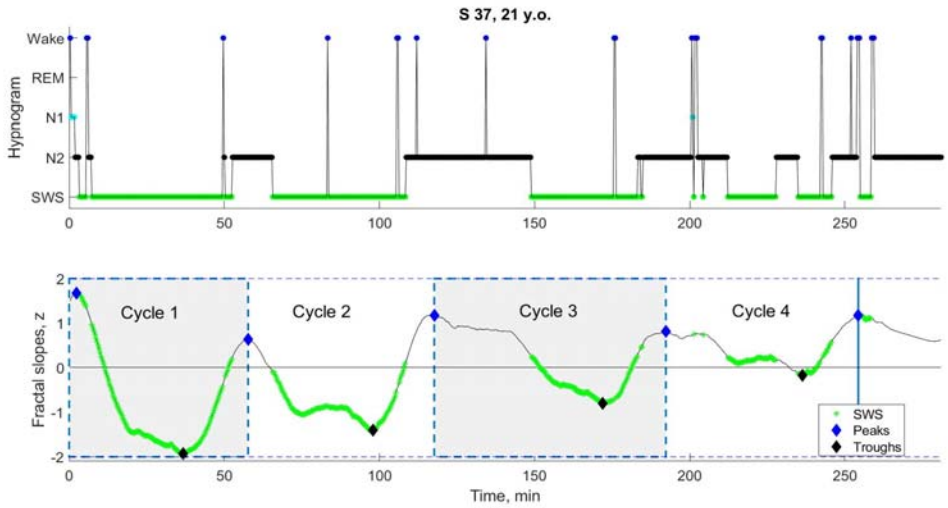


Figure 9. Cycles with skipped REM sleep. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top) observed in three young participants (from Dataset 4). Hypnograms show skipped first cycles (as well as the rest of the classical cycles). In S17, at the 90th minute, an episode of REM sleep is expected to appear – except only a "lightening of sleep" (wake, N1 and N2) is observed. We divided the long 209-minute cycle into two cycles, the 90-minute skipped cycle and the 119-minute normal cycle. In S18, at the 63rd minute, an episode of REM sleep is expected to appear – except only a "lightening of sleep" (N1 and N2) is observed. We divided the long 138-minute cycle into two cycles, the 63-minute skipped cycle and the 75-minute normal cycle. The fractal cycle algorithm was very effective in detecting skipped cycles, showing a one-to-one match with divided – but not long undivided – cycles. S37's hypnogram shows that she has no REM sleep at all, i.e., all her cycles are the "skipped" ones. Based on this, S37 was even excluded from the formal analysis. This example is nevertheless presented here to illustrate that the fractal cycle algorithm is sensitive enough in detecting sleep cycles even in the absence of REM sleep.

Age and fractal cycles

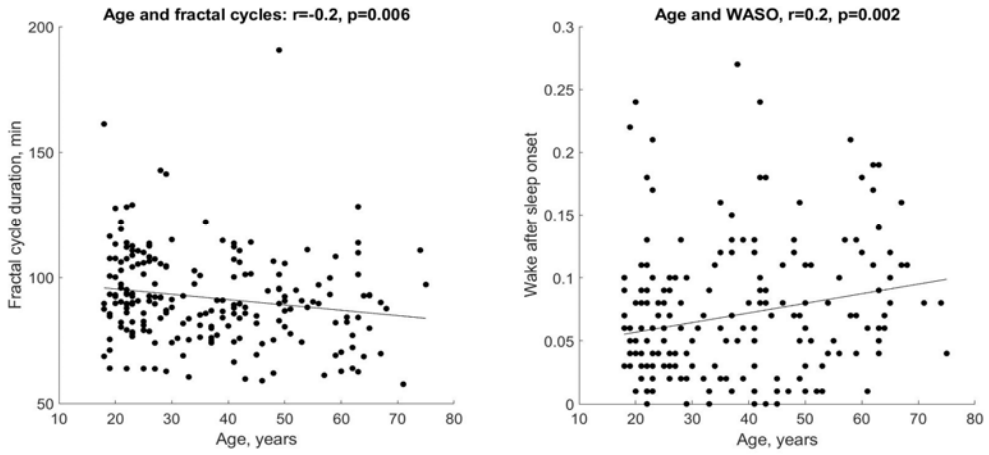
We found that in the merged adult dataset (Datasets 1 – 5, n = 205), the mean duration of the fractal cycles negatively correlated with the age of the participants (r = -0.19, p = 0.006, age range: 18 – 75 years, median: 33.5 years, Fig. 10 top left). Intriguingly, this correlation looked like a mirror image of the correlation between the age and wakefulness after sleep onset (Fig. 10 top right). Following this observation, we performed an additional correlation between the

fractal cycle duration and wakefulness proportion and found that it was non-significant (r = 0.01, p = 0.969). Nevertheless, we further performed a partial correlation between the fractal cycle duration and participant age, while controlling for the effect of wakefulness after the sleep onset and found that the correlation remained significant (r = -0.18, p = 0.011).

Given that participant's age also correlated with REM latency (Fig.10 bottom right) while REM latency further correlated with fractal cycle duration (Fig.10 bottom left), we performed an additional partial correlation between the fractal cycle duration and age while controlling for REM latency. We found that it remained significant (r = -0.16, p = 0.025). The partial correlation between the fractal cycle duration and REM latency adjusted for the participant's age was non-significant (r = 0, p=0.746).

Of note, these correlations were significant while analyzing the pooled dataset only, they were not observed while analyzing each dataset separately. Moreover, when we added to the pooled adult dataset (Datasets 1 – 5) our pediatric dataset (Dataset 6), the correlation between fractal cycle duration and age became non-significant.

Interestingly, the mean duration of the classical cycles did not correlate with the age of the adult participants neither in the merged dataset (r = -0.02, p = 0.751) nor while analyzing each dataset separately.



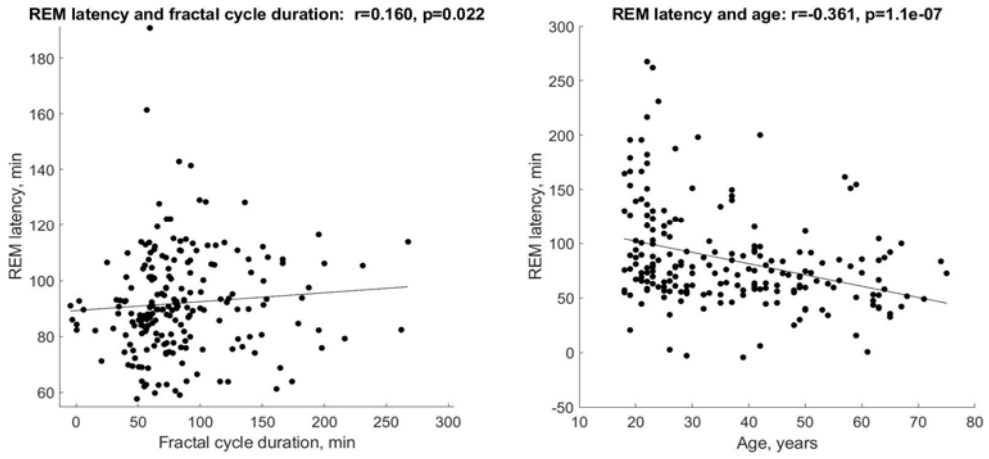


Figure 10. Correlations. Top left: Fractal cycle duration negatively correlates with the age of healthy participants. **Top right:** The WASO proportion positively correlates with the age of healthy participants. The partial correlations between the fractal cycle duration and age adjusted for WASO and REM latency remained significant. **Bottom left:** Fractal cycle duration positively correlates with REM latency of the healthy participants. **Bottom right:** REM latency negatively correlates with the participant's age. The partial correlation between the fractal cycle duration and REM latency adjusted for the participant's age is non-significant. Age range: 18 – 75 years, median: 33.5 years, n = 205 (pooled Datasets 1 – 5), raw (non-ranked) values are presented, r – Spearman's correlation coefficient where values < 0.3 are considered as weak correlations, REM – rapid eye movement, WASO – wakefulness after sleep onset.

Fractal cycles in MDD

Patients at 7- and 28-day of medication treatment as well as long-termed medicated patients (Datasets A – C) showed a longer fractal cycle duration compared to controls with medium effect size (Table 3, Fig.11). Moreover, in Dataset B, the patients who took REM-suppressive antidepressants (See Supplementary Table 5 of Supplementary Material 2 for information on specific medications taken by the patients) showed longer fractal cycle duration compared to patients who took REM-non-suppressive antidepressants with medium effect size (70 cycles of 21 patients vs 63 cycles of 17 patients). In Dataset C, no difference was detected between these sub-groups. However, it should be noted that in Datasets C, the REM-suppressive and REM-non-suppressive antidepressant groups were unbalanced (87 cycles of 23 patients vs 35 cycles of 10 patients) and consisted of different medications than Dataset B.

Table 3, Fig.11 and Fig.12 show results calculated over frontal electrodes (or central ones for Dataset A). The topographical analysis over other areas is reported in Supplementary Table 6 of Supplementary Material 2.

Table 3: Fractal cycles in MDD

Dataset	Group	No. participants	Age	Classical cycles				Fractal cycles				Fractal-classical cycles correlation	
				No. cycles	Duration, min	p	Cohen's d	No. cycles	Duration, min	p	Cohen's d	r	p
A	HC (Dataset 1)	38	46.8 ± 10.7	171	86 ± 23	---	---	167	84 ± 35	---	---	0.33	0.042
	long-termed med. MDD	40	50.1 ± 8.6	141	109 ± 55	10^{-6}	0.6	143	97 ± 43	0.001	0.3	0.51	0.001
B	HC (Dataset 2)	39	31.0 ± 9.9	180	90 ± 21	---	---	171	90 ± 26	---	---	0.51	0.001
	unmed. MDD	38	31.3 ± 10.2	169	92 ± 31	n.s.	---	155	92 ± 38	n.s.	---	0.19	n.s.
	7d med. MDD	---	---	149	102 ± 43	0.003	0.4	133	107 ± 51	10^{-4}	0.5	0.68	10^{-6}
	REM-non-suppressive	17	31.6 ± 10.4	77	91 ± 26	---	---	63	95 ± 44	---	---	0.49	0.046
	REM-suppressive	21	33.6 ± 11.3	72	103 ± 54	0.002*	0.5*	70	121 ± 55	0.003*	0.5*	0.66	0.001
C	HC (Dataset 3)	32	45.3 ± 15.9	146	89 ± 23	---	---	154	88 ± 32	---	---	0.57	0.001
	7d med. MDD	33	46.2 ± 16.2	121	114 ± 45	10^{-7}	0.7	122	107 ± 48	10^{-4}	0.5	0.47	0.006
	28d med. MDD	---	---	117	111 ± 51	10^{-5}	0.6	100	106 ± 51	0.001	0.4	0.42	0.018

*MDD – major depressive disorder, unmed. – unmedicated, med. – medicated, HC – healthy controls, p – p-values of the non-parametric test comparing a given group to HC, * – compared to the non-REM suppressive antidepressant group, r – Pearson's correlation coefficient.*

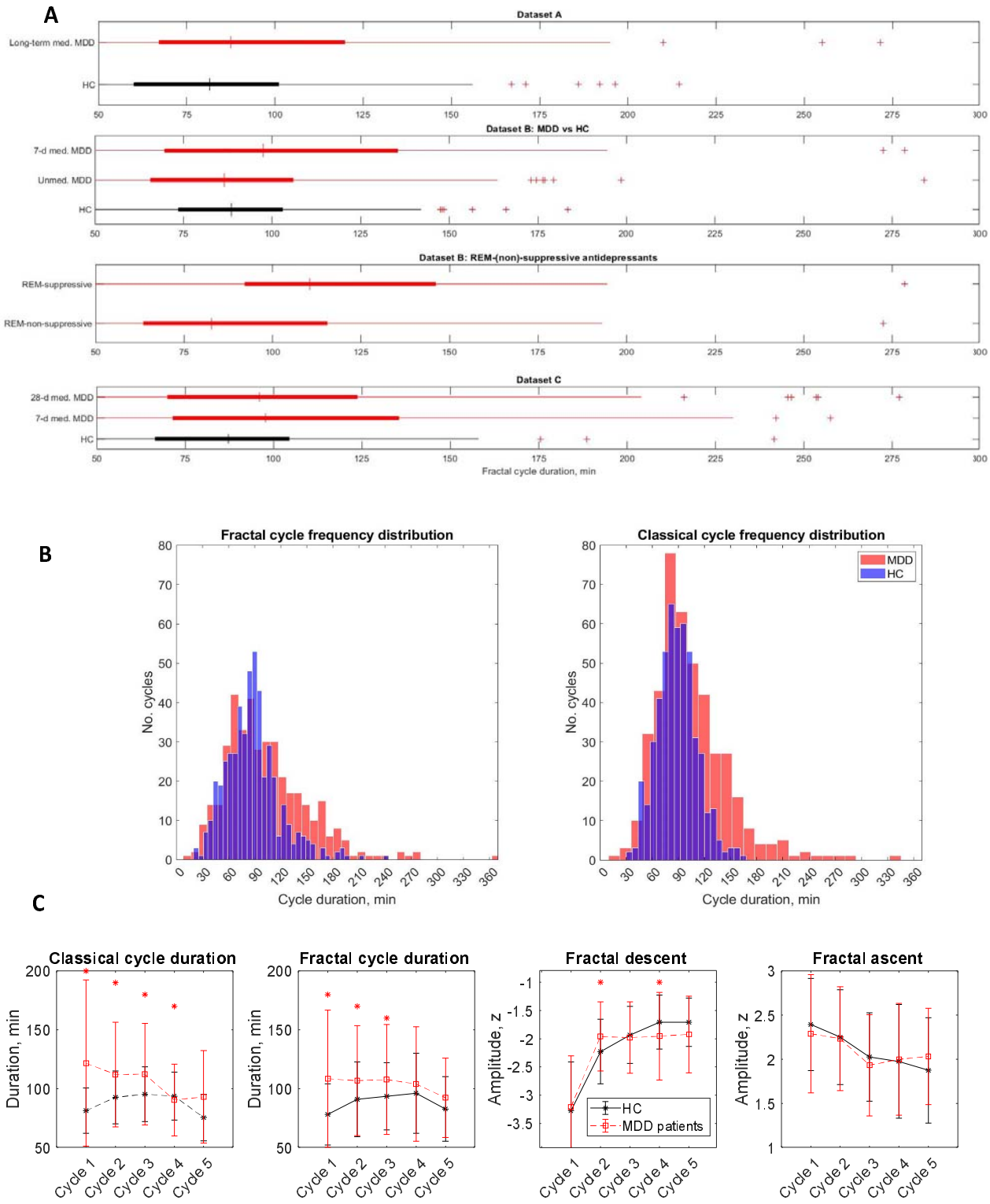


Figure 11. Fractal cycle duration in MDD vs HC. A. Box plots. The fractal cycle duration is longer in medicated MDD patients (red) compared to age and gender-matched healthy controls (black) in all datasets. In Dataset B, fractal cycles are longer in the medicated vs patients' own

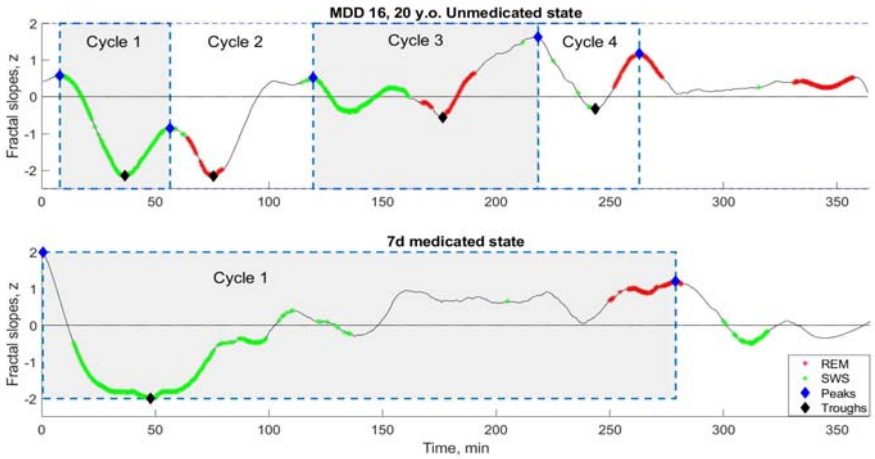
unmedicated state and in patients who took REM-suppressive vs REM-non-suppressive antidepressants. A vertical central line represents the median in each box, the left and right edges of the box indicate the 25th and 75th percentiles, respectively, the whiskers extend to the most extreme data points not considered outliers, and a plus sign represents outliers (individual cycles). **B. Frequency distribution.** Individual fractal and classical cycles pooled from three MDD datasets (A – C) are counted separately for medicated MDD patients and HC. MDD – major depressive disorder, HC – healthy controls, unmed. – unmedicated, med. – medicated. **C. Overnight dynamics.** Cycle-to-cycle dynamics of the duration of both fractal and classical cycles show a gradual decrease in medicated patients vs an inverted U shape in controls. The between-group difference in cycle duration is the largest for the first cycle. Patients show flatter fractal descents of the second cycle and steeper fractal descents of the fourth cycle compared to controls. Contrary to controls, patients do not show a gradual decrease in absolute amplitudes of the fractal descents from the second to the fourth cycles. Patients and controls show comparable cycle-to-cycle dynamics of fractal ascents, * marks a statistically significant difference between the groups.

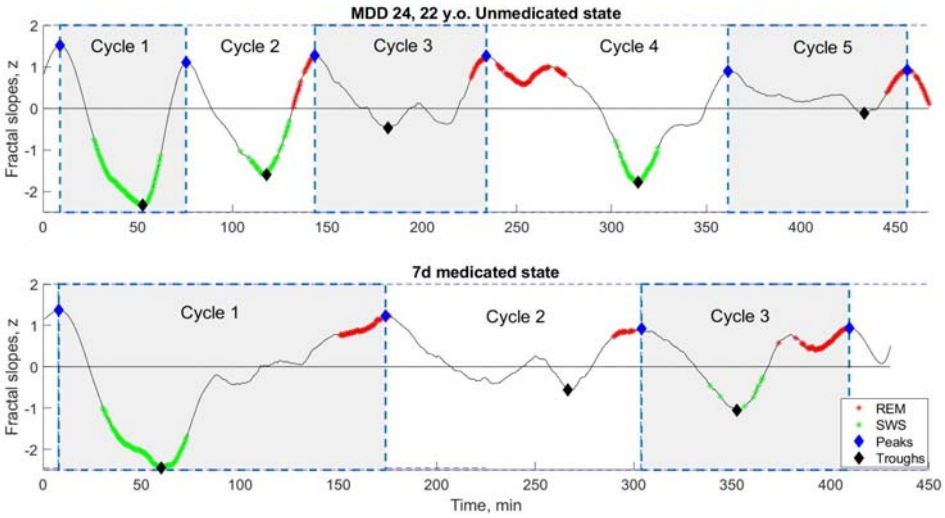
In Dataset B (the only dataset including unmedicated patients), 7-day medicated patients had longer fractal cycles compared to their own unmedicated state with medium effect size ($p = 0.001$, Cohen's $d = 0.4$, Fig. 11 – 12). Unmedicated patients and controls showed comparable durations of the fractal cycles. The only difference observed between these groups was a smaller amplitude of the fractal descent of the first fractal cycles in unmedicated patients compared to controls with a medium effect size (-3.2 vs -3.6 z, $p = 0.040$, Cohen's $d = 0.5$).

In a pooled dataset, medicated patients showed a prolonged duration of fractal cycles compared to the controls (104 ± 49 vs 88 ± 31 min, $p < 0.001$, Fig.11 B). The between-group difference was the largest for the first cycle (Fig.11 C). Moreover, cycle-to-cycle overnight dynamics of the fractal cycle duration showed a gradual decrease in medicated patients vs an inverted U shape in controls (Fig.11 C).

To test our hypothesis that fractal cycles are more sensitive than classical cycles in detecting differences between patients and controls, we performed the same analysis as described above while using the duration of classical cycles as the variable of interest. The resul ts were similar

to those obtained for fractal cycle durations (Table 3, Fig.11 B – C), i.e., our hypothesis was not confirmed. The comparable outcomes of the two analyses can be explained by the positive correlations between the durations of fractal and classical cycles observed in all groups of the medicated MDD patients like that seen in healthy controls (Table 3).


MDD 16, 20 y.o. Unmedicated state
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Fractal slopes, z
7d medicated state
Cycle 1
REM
SWS
Peaks
Troughs
Time, min


MDD 24, 22 y.o. Unmedicated state
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Fractal slopes, z
7d medicated state
Cycle 1
Cycle 2
Cycle 3
REM
SWS
Peaks
Troughs
Time, min

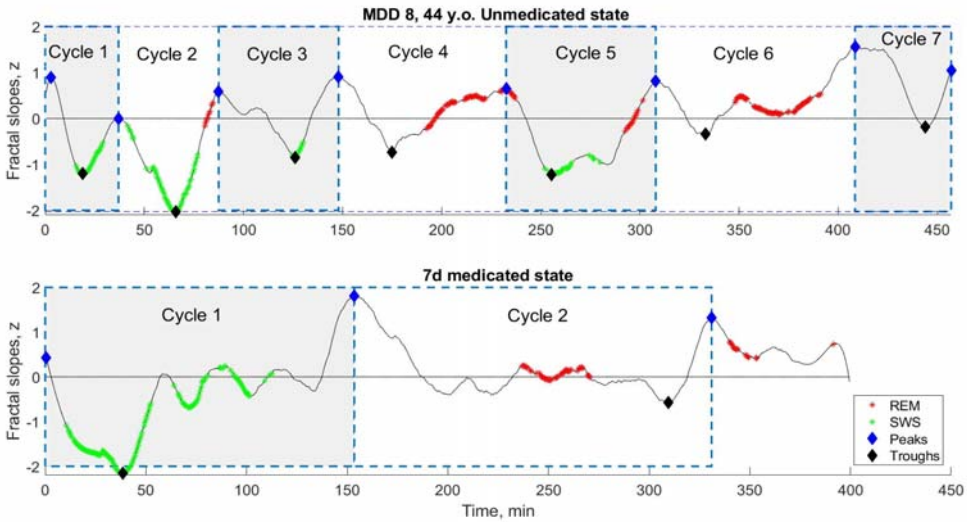

MDD 8, 44 y.o. Unmedicated state
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7
Fractal slopes, z
7d medicated state
Cycle 1
Cycle 2
REM
SWS
Peaks
Troughs
Time, min

Figure 12. Individual fractal cycles of sleep in MDD. Time series of smoothed z-normalized fractal slopes observed in three MDD patients in their unmedicated (top) and 7-day medicated (bottom) states. Peaks (blue diamonds) are defined with the Matlab function *findpeaks* with the minimum peak distance of 20 minutes and minimum peak prominence of 0.9 z. Fractal cycles duration (defined as an interval of time between two successive peaks) is longer in the medicated compared to unmedicated states, reflecting shallower fluctuations of fractal (aperiodic) activity. MDD – major depressive disorder, SWS – slow-wave sleep, REM – rapid eye movement.

Discussion

This study introduced the new concept of "fractal cycles" of sleep, which is based on temporal fluctuations of the fractal (aperiodic) slopes across a night. We showed that durations of these "fractal cycles" correlated with those of classical (non-REM – REM) sleep cycles defined by hypnograms in five independently collected datasets counting 205 healthy participants overall as well as in 111 medicated patients with MDD. Overnight cycle-to-cycle dynamics in healthy adults showed an inverted U-shape for both fractal and classical cycle durations. The fractal cycle algorithm was effective in detecting cycles with skipped REM sleep. The findings further revealed that children and adolescents showed shorter fractal cycles as compared to young healthy adults. In adults, fractal cycle durations negatively correlated with participants' age. Medicated patients with MDD showed longer fractal cycles compared to their own unmedicated state and healthy controls. Below we discuss these findings in detail.

Fractal cycles: definition and motivation

We observed that the time series of fractal slopes have a cyclical nature, descending and ascending for about 4 – 6 times per night with a mean duration of approximately 90 minutes for each such ("fractal") cycle. This strikingly resembles the description of classical sleep cycles. Indeed, both the visual inspection and formal correlational analyses revealed that the timing and duration of the fractal and classical cycles mainly matched. This led us to propose that ***the "fractal cycles of sleep" could serve as a new data-driven definition of sleep cycles***, i.e., a

means to appreciate quantitatively what has been previously observed only qualitatively using hypnograms.

Notably, we do not claim that fractal cycles are a substitute for the study of the individual sleep stages or microstructural features of sleep. We want to stress, however, that currently, sleep research is shifted towards the study of, to use a metaphor, "the atoms" of sleep, such as individual sleep stages, slow oscillations, spindles, microarousals etc. Yet it is possible that some important (currently unknown) features of sleep could be explored only at the level of sleep cycles, "the molecules of sleep". (Note, that we use the molecule and atom concepts only as a metaphor for the macro- and microstructure of sleep.)

Hypothetical functional significance of aperiodic activity and fractal cycles

The decision to incorporate fractal activity analysis in sleep cycle research was based on the reports that fractal (aperiodic) dynamics may reflect the bistability of the network (the overall tendency of alternating up and down states) (Baranauskas et al., 2012) and/or alterations in the balance between neural excitatory and inhibitory currents (Gao et al., 2017). Circumstantial evidence suggests that fractal activity is a measure of sleep homeostasis or sleep intensity, reflecting sleep-wake history, sleep stage differences, sleep cycles, age-effects, local sleep and sleep disorders (Bódizs et al., 2023). Recently, it has been reported that during human sleep, spectral slopes positively correlate with pupil size, a marker of arousal levels linked to the activity of the locus coeruleus-noradrenergic system (Carro-Domínguez et al., 2023).

According to the reciprocal-interaction model of sleep cycles, each sleep phase is characterized by a specific neurochemical mixture. During non-REM sleep, aminergic inhibition decreases and cholinergic excitation increases such that at REM sleep onset, aminergic inhibition is shut off and cholinergic excitability reaches its maximum, while other outputs are inhibited (Pace-Schott & Hobson, 2002). Complex inhibitory and excitatory connections between pontine REM-on and REM-off neurons are further modulated by such neurotransmitters as GABA, glutamate, nitric oxide and histamine. Intriguingly, during REM sleep, acetylcholine plays the main role in

maintaining brain activation, which is expressed as EEG desynchronization, one of the main features of REM sleep, and other systems are silent (Nir & Tononi, 2010). This suggests that acetylcholine, which fluctuates cyclically across a night as a result of the REM-off – REM-on interactions, might have a key role in the sleep phase alternation.

Given that the specific neurochemical milieu of the brain produces a specific type of conscious experience (Nir & Tononi, 2010) and that conscious experience was shown to be related to fractal activity derived from the human sleep EEG (Colombo et al., 2019), it is tempting to speculate that fractal activity tracks sleep-related changes in the neurochemical milieu of the brain and overall network dynamics. This has not been tested in humans; nevertheless, in rats, cholinergic nucleus basalis stimulation acutely increased higher to lower frequency cortical LFP power ratio or in other words, caused flattering of spectral decay (Goard & Dan, 2009). One can, therefore, speculate that ascending parts and peaks of fractal cycles coincide with acetylcholine release. The troughs of fractal cycles, in turn, might reflect a higher homeostatic pressure and even cause feelings of sleepiness and the search for the opportunity of initiating sleep, as these are periods of the steepest fractal activity, which implies a higher ratio of lower over higher frequency power in the EEG (Bódizs et al., 2023).

In view of this literature, we speculate that fractal fluctuations may reflect two antagonistic roles of sleep (Simor et al., 2022). Specifically, fractal cycle troughs might cohere with sensory disconnection that facilitates restorative properties of sleep while fractal cycle peaks reflect monitoring of the environment that transiently restores alertness (Table 4).

Table 4: Hypothetical functional significance of fractal cycles

Theory/model	Reference	Hypothetical integration of the fractal cycle concept to the existing model
Two antagonistic roles of sleep: 1) sensory disconnection that facilitates restorative properties of sleep; 2) monitoring of the environment that transiently restores alertness.	Simor et al., 2022	- troughs of fractal cycles reflect 1); - peaks of fractal cycles reflect 2).
Reactive and predictive homeostatic functions of sleep: 1) intensive restorative processes during early-night sleep; 2) active future-oriented processes during late-night sleep.	Simor et al., 2023	- deeper fractal cycles observed during early-night sleep reflect 1); - shallower fractal cycles seen during late-night sleep reflect 2).
Reciprocal-interaction model of sleep cycles: - alternations between non-REM and REM sleep stages are explained by the interaction between aminergic and cholinergic neurons of the mesopontine junction.	Pace-Schott & Hobson, 2002	- ascents and peaks of fractal cycles reflect acetylcholine release*; - descents and troughs of fractal cycles coincide with aminergic activity.
Noradrenergic neurons create a non-reducible timeframe for the NR	Osorio-Forero	Ascents and peaks of fractal cycles reflect a cease of

EM-REM sleep cycle where low noradrenaline levels allow entries into REM sleep.	et al., 2023.	noradrenaline release.
The Neuronal Transition Probability Model: 1) During a move towards deep sleep beta power drops exponentially, delta power rises in an S-curve and sigma power peaks while delta is still rising; 2) During a move away from deep sleep, delta drops, beta rises.	Merica & Fortune, 2011	- descending part of the fractal cycle corresponds to 1); - ascending part of the fractal cycle corresponds to 2).

** this hypothesis is also based on the report that in rats, cholinergic nucleus basalis stimulation caused flattering of spectral decay (Goard & Dan, 2009).*

Fractal and classical cycles comparison

In this study, in healthy adults, 81% of all fractal cycles defined by our algorithm could be matched to individual classical cycles defined by hypnograms. Correlations between the durations of fractal and classical cycles were observed not only in healthy adults but also in medicated patients with MDD. The results show that displaying sleep data using fractal activity as a function of time meaningfully adds to the conventionally used hypnograms thanks to the gradual and objective quality of fractal power.

Thus, in hypnograms, each sleep stage is ascribed with a rather arbitrary assigned categorical value (e.g., wake=0, REM=-1, N1=-2, N2=-3 and SWS=-4, Fig.2), which, therefore, has little biological foundation and even somewhat contradicts the gradual nature of typical biological processes. Moreover, categorical labeling of sleep stages induces information loss and can lead to several misinterpretations, such as an implied order of sleep stages (e.g., “REM sleep is located between wake and N1”) and an implied “attractor state” conception of sleep stages (e.g., “no inter-stage states”). Likewise, defining the precise beginning and end of a classical

sleep cycle using a hypnogram is often difficult and arbitrary, for example, in cycles with skipped or interrupted REM sleep or REM sleep without atonia.

In contrast, fractal cycles do not rely on the assignment of categories, being based on a real-valued metric with known neurophysiological functional significance. This introduces a biological foundation and a more gradual impression of nocturnal changes compared to the abrupt changes that are inherent to hypnograms. Likewise, fractal cycle computation is automatic and thus objective. Moreover, fractal cycle algorithm can detect cycles with skipped REM sleep, i.e., the cycles where only a "lightening of sleep" occurs, presumably due to too high non-REM sleep pressure (Le Bon, 2020). Such cycles are common in children, adolescents and young adults. We think that the ability of our algorithm to detect skipped cycles via these lightenings is one of its most significant methodological strengths. We further speculate that fractal cycles might be useful in clinical settings, for example, as a means to detect REM sleep without atonia episodes in REM sleep behaviour disorder, the episodes currently often mistaken as non-REM sleep.

In summary, we expect that fractal cycles could bring insights into (yet) unexplained phenomena thanks to their gradual and objective quality, and, therefore, have the potential to induce a paradigm shift in basic and clinical (see below) sleep research.

Fractal slopes and SWA: overnight dynamics

Of note, currently, the gold standard marker of many sleep functions (e.g., restorative, regenerative) with a long-standing use is slow-wave activity (SWA), which, similar to fractal slopes, is also continuous and objective. SWA, however, has several disadvantages, such as large variability between individuals, which makes it impossible to set up a given reference point for healthy sleep (Horváth et al., 2022). Interindividual variability of spectral slopes is much smaller compared to SWA, making it a less individual-specific metric, yet spectral slopes strongly correlate with SWA (31 – 53% of shared variance throughout the NREM periods) (Horváth et al., 2022; Bódizs et al., 2023). In addition, both the literature and our findings show

that while SWA has a cycling nature during the first part of the night, neural dynamics of late-night's sleep are not reflected by SWA at all (Fig. S5 in Supplementary Material 2). Given that SWA is a primary marker of sleep homeostasis, this pattern possibly reflects the dissipation of a sleep need during the course of night sleep (Bódizs et al., 2023). In contrast, fractal slopes show a cycling nature over the entire night's sleep (Fig.2), suggesting that they are a more suitable means to reflect the macrostructure of the whole night's sleep than SWA.

Having said this, we should highlight that characteristics of fractal cycles of sleep do undergo some overnight changes. Thus, the durations of both fractal and classical cycles in health show an inverted U-shape across a night and the amplitudes of fractal descents and ascents are larger during early-night- compared to late-night cycles (Fig.4C). This is in line with the report on the flattening of fractal activity from early to late sleep cycles (Horváth et al., 2023). If seen in the context of the reactive and predictive homeostatic functions of sleep (Simor et al., 2023), deeper fractal cycles observed during early-night sleep could reflect intensive restorative processes (which are also reflected by SWA), whereas shallower fractal cycles seen during the later part of night's sleep could reflect more active future-oriented processes (which are not reflected by SWA) with a shift towards neural excitation relative to inhibition expressed as overall flatter fractal activity (Table 4).

Fractal cycles and age

We found that older healthy participants had shorter fractal cycles compared to the younger ones while classical cycles did not correlate with the participants' age. At first glance, it looked as if this association simply reflected an increased proportion of the wake after the sleep onset often seen in older adults (Fig.10 top). Indeed, our algorithm does not discriminate between the smoothened wake- and REM-related fractal slopes and can define both as local peaks (Fig.6). This happens because for the most part, wake- and REM sleep-related smoothed fractal slopes display comparable values, which are also the highest ones compared to other stages (Fig. S2, green squares, Supplementary Material 2). Since the fractal cycle duration is defined as

an interval of time between two adjacent peaks, more awakenings during sleep are expected to result in more peaks and, consequently, more fractal cycles per total sleep time, i.e., a shorter cycle duration. (It is worth mentioning that unsmoothed wake- and REM-related slopes differ (Schneider et al., 2022 and Fig. S2 here (black squares). However, this is a side notion as raw values were not used in this study since our algorithm performed poorly on raw time series).

Intriguingly, the replacement of wake-related values with NaNs did not change the results. Similarly, the partial correlation between fractal cycle duration and age remained significant after controlling for the amount of wake after sleep onset. This hints that the association between fractal cycles and age might reflect more than just a confounding effect of the amount of wake after sleep onset. This interpretation is in line with literature on age-related changes in aperiodic activity, namely, on flattering of fractal slopes with age (Voytek et al., 2015; Bódizs et al., 2021; Pathania et al., 2022), especially during SWS (Schneider et al., 2022). Likewise, aging is associated with shorter and fewer classical cycles, with a mean of 3.5 cycles per night compared to the usual 4 – 5 in adults and adolescents (Conte et al., 2014). Our findings suggest that fractal cycles are more sensitive to these age-related alterations than the classical ones. We further speculate that the claim that "age affects sleep microstructure more than sleep macrostructure" (Schwarz et al., 2017) might reflect the lack of a reliable measure of sleep cycles.

Another plausible explanation for longer fractal cycles in younger compared to older adults could be rooted in increased sleep intensity of the younger adults (Jenni & Carskadon, 2004). Further, high sleep intensity driven by homeostatic pressure is associated with the delay in the emergence of the REM sleep phase (Le Bon, 2020; Tarokh et al., 2012). In our dataset, REM latency also decreased with age. Thus, Fig. 10 (bottom right) illustrates that young adults might present with very delayed REM latency, i.e., 200 – 250 minutes after sleep onset, in line with the notion that younger adults more often show cycles with skipped REM sleep (Fig.9). This can be partly explained by the fact that younger people often have a later chronotype ("night owls") than older people with puberty linked to delays in the sleep cycle by up to 2 hours

(Randler et al., 2016). Young people also have a longer circadian rhythm (> 24 h) than older ones (< 24 h, Monk et al., 2005).

To further strengthen this line of explanations, we performed a supplemental analysis, which showed that prolonged REM latencies are indeed associated with longer fractal cycles (Fig.10 bottom left). Nevertheless, the correlation was weak (yet significant) and observed in the pooled dataset only, i.e., not while analyzing individual datasets. Likewise, the partial correlation between the fractal cycle duration and REM latency adjusted for the participants' age was non-significant. Moreover, we found that children and adolescents (the group that has the longest REM latencies and the highest rate of cycles with skipped REM sleep) showed shorter fractal cycles compared to young adults, specifically the early-night fractal cycles. In view of these analyses, our attempt to explain longer fractal cycles in younger compared to older adults by increased REM sleep latency becomes less convincing. Moreover, given that our algorithm does not miss "skipped" cycles, longer REM sleep latencies should not necessarily be related to longer cycles. To summarize, at this stage, the mechanism underlying age-related differences in fractal cycle duration is unclear (possibly with some non-linearities) and future studies are needed to corroborate and further explore it.

Fractal cycles in MDD

In addition, our study shows that deviations from the observed fractal patterns have some clinical relevance. We found that MDD patients in the medicated state had longer fractal cycles compared to their own unmedicated state and healthy controls. The largest differences were observed for the first sleep cycles. Moreover, patients who took REM-suppressive antidepressants showed prolonged fractal cycles compared to patients who took REM-non-suppressive antidepressants. Given that the fractal cycle duration was defined as an interval of time between two adjacent peaks and that the peaks usually coincide with REM sleep (Fig.2), this finding may reflect such aftereffects of antidepressants as delayed onset and reduced amount of REM sleep (Palagini et al., 2013). In other words, if a patient has fewer REM sleep

episodes, then the time series of their fractal slopes has fewer peaks and the algorithm detects fewer cycles per total sleep time, i.e., cycle's duration is longer (Fig.11).

Another explanation considers our previous finding that medicated MDD patients show flatter average fractal slopes compared to controls and their own unmedicated state during all sleep stages (Rosenblum et al., 2023 a). This might mean that the antidepressant intake results in shallower fractal fluctuations, which in turn implies that fewer peaks could be detected by our algorithm as the peak threshold was defined *a priori* in a healthy – not MDD – sample. Interestingly, recently, flatter fractal slopes during REM sleep have been also associated with sustained polyphasic sleep restriction in health (Rosenblum et al., 2023 d), whereas flatter fractal slopes during NREM sleep were observed in patients with objective insomnia and sleep state misperception, reflecting an abnormally high level of excitation in line with the hyperarousal model of insomnia (Andrillon et al., 2020).

Limitations and strengths

The major limitation of this study is its correlational approach, and thus an inability to shed light on the mechanism underlying sleep cycle generation. Therefore, the question of what determines the number and duration of cycles per night remains open. Moreover, further work is needed to determine the mathematically precise and physiologically meaningful model of fractal cycles. Notably, here, we suggest that fractal cycles are a new tool to study the macrostructure of sleep; however, they are presumably not a substitute for the study of the individual sleep stages and microstructural features of sleep (e.g., microarousals, spindles, slow waves).

Additionally, we explored the effect of developmental changes and aging on fractal cycles using a cross-sectional observational approach, whereas these factors might be disentangled more precisely in a longitudinal approach. The age of the pediatric group ranged from 8 – 17 years old; studying younger children and babies would add crucial information on the influence of neurodevelopmental changes on fractal cycles.

The strengths of this study are its large sample size, scripts and data sharing and self-replications in several clinical and healthy datasets of participants in a broad age range, affirming the overall robustness of the phenomena of fractal cycles. Another strength of this work is its generalizability as it has shown that the studies conducted in different experimental environments (including one study conducted at home) using different EEG devices provide comparable results.

To summarize, the large sample and self-replication performed in this study suggest that the "fractal cycle" is a universal concept that should be extensively studied. Displaying the data in the format of fractal cycles provides an intuitive and biologically plausible way to present whole-night sleep neural activity and also adds some graduality to the purely categorical concept of sleep stages that comprise a hypnogram. In future studies, this graduality might help to illuminate differences in sleep architecture across different species, advance our understanding of the role of sleep in neurocognitive development in infants and adolescents as well as in neurodegenerative processes and other fields of neuroscience.

Conclusion

We observed that the slopes of the fractal (aperiodic) spectral power descend and ascend cyclically across a night such that the peaks of the time series of the fractal slopes coincide with REM sleep or sleep "lightening" while the troughs of these time series coincide with non-REM sleep. Based on this observation, we introduced a new concept, the "fractal cycle" of sleep, defining it as a time interval between two adjacent local peaks of the fractal time series. We have shown that fractal cycles defined by our algorithm largely coincide with classical (non-REM – REM) sleep cycles defined by a hypnogram and replicated our findings in several independently collected healthy and clinical datasets. Moreover, we found that the fractal cycle algorithm reliably detected cycles with skipped REM sleep. In addition, we observed that fractal cycle duration changes as a non-linear function of age, being shorter in children and

adolescents compared to young adults as well as in older compared to younger adults. To this end, we conclude that the fractal cycle is an objective, quantifiable and universal concept that could be used to define sleep cycles and display the whole-night sleep neural activity in a more intuitive and biologically plausible way as compared to the conventionally used hypnograms. Having shown that the fractal cycles are prolonged in medicated patients with MDD, we suggest that fractal cycles are a useful tool to study the effects of antidepressants on sleep. Possibly, fractal cycles also will be able to serve as a means to explore sleep architecture alterations in different clinical populations (e.g., to detect REM sleep without atonia) and during neurocognitive development. In summary, this study shows that the fractal cycles of sleep are a promising research tool relevant in health and disease that should be extensively studied.

Data and code availability

The original contributions presented in the study are available under https://osf.io/gxzyd/. Further inquiries can be directed to the corresponding author.

Acknowledgments

This publication has been supported by the Dutch Research Council (NWO), the National Research, Development and Innovation Fund of the Ministry of Innovation and Technology of Hungary (TKP2021- EGA-25 and ÚNKP-22-3-II), Swiss National Science Foundation (grants number 320030_153387, 320030_179443), and the HMZ Flagship grant "SleepLoop" of the University Medicine Zurich, Switzerland. We acknowledge that the Child Development Center, University Children's Hospital Zürich, University of Zürich is the source of the pediatric data (here, referred to as "Dataset 6"). Namely, we would like to thank Carina Volk, Valeria Jaramillo, Renato Merki and Mirjam Studler for the collection of the pediatric data.

Author contributions

YR and MD designed and conceptualized the study. YR analyzed the data and wrote the manuscript. YR had full access to all datasets reported in the study. All authors contributed to, reviewed, and approved the final draft of the paper. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

The authors declare no competing interests.

References

American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 3rd ed. 2014.

Andrillon T, Solelhac G, Bouchequet P, Romano F, Le Brun MP, Brigham M, Chennaoui M, Leger D. Revisiting the value of polysomnographic data in insomnia: more than meets the eye. Sleep medicine. 2020 Feb 1;66:184-200. https://doi.org/10.1016/j.sleep.2019.12.002

Baranauskas G, Maggiolini E, Vato A, Angotzi G, Bonfanti A, Zambra G, Spinelli A, Fadiga L. Origins of 1/f2 scaling in the power spectrum of intracortical local field potential. Journal of Neurophysiology. 2012 Feb;107(3):984-94. https://doi.org/10.1152/jn.00470.2011

Bódizs R, Schneider B, Ujma P, Horváth C, Dresler M, Rosenblum Y. Fundamentals of Sleep Regulation: Model and Benchmark Values for Fractal and Oscillatory Neurodynamics. 2023. Available at SSRN: http://dx.doi.org/10.2139/ssrn.4584491

Bódizs R, Szalárdy O, Horváth C, Ujma PP, Gombos F, Simor P, Pótári A, Zeising M, Steiger A, Dresler M. A set of composite, non-redundant EEG measures of NREM sleep based on the power law scaling of the Fourier spectrum. Scientific reports. 2021 Jan 21;11(1):1-8. https://doi.org/10.1038/s41598-021-81230-7

Bovy L, Weber FD, Tendolkar I, Fernández G, Czisch M, Steiger A, Zeising M, Dresler M. Non-REM sleep in major depressive disorder. NeuroImage: Clinical. 2022 Jan 1;36:103275. https://doi.org/10.1016/j.nicl.2022.103275

Buzsaki G. Rhythms of the Brain. 2006. Oxford University Press.

Campbell IG, Darchia N, Higgins LM, Dykan IV, Davis NM, Bie ED, Feinberg I. Adolescent changes in homeostatic regulation of EEG activity in the delta and theta frequency bands during NREM sleep. Sleep. 2011 Jan 1;34(1):83-91. https://doi.org/10.1093/sleep/34.1.83

Carrier J, Viens I, Poirier G, Robillard R, Lafortune M, Vandewalle G, Martin N, Barakat M, Paquet J, Filipini D. Sleep slow wave changes during the middle years of life. European Journal of Neuroscience. 2011 Feb;33(4):758-66. https://doi.org/10.1111/j.1460-9568.2010.07543.x

Carro-Domínguez M, Huwiler S, Oberlin S, Oesch TL, Badii G, Lüthi A, Wenderoth N, Meissner SN, Lustenberger C. Pupil size reveals arousal level dynamics in human sleep. bioRxiv. 2023:2023-07. https://doi.org/10.1101/2023.07.19.549720

Colombo MA, Napolitani M, Boly M, Gosseries O, Casarotto S, Rosanova M, Brichant JF, Boveroux P, Rex S, Laureys S, Massimini M. The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. *NeuroImage*. 2019;189:631-44. https://doi.org/10.1016/j.neuroimage.2019.01.024

Conte F, Arzilli C, Errico BM, Giganti F, Iovino D, Ficca G. Sleep Measures Expressing 'Functional Uncertainty'in Elderlies' Sleep. Gerontology. 2014 Apr 10;60(5):448-57. https://doi.org/10.1159/000358083

Courtet P, Olié E. Circadian dimension and severity of depression. European Neuropsychopharmacology. 2012 Jan 1;22:S476-81.

Donoghue T, Haller M, Peterson EJ, Varma P, Sebastian P, Gao R, Noto T, Lara AH, Wallis JD, Knight RT, Shestyuk A. Parameterizing neural power spectra into periodic and aperiodic components. Nature neuroscience. 2020 Dec;23(12):1655-65. https://doi.org/10.1038/s41593-020-00744-x

Feinberg I. Changes in sleep cycle patterns with age. Journal of psychiatric research. 1974 Oct 1;10(3-4):283-306.

Feinberg I, Floyd Tl. Systematic trends across the night in human sleep cycles. Psychophysiology. 1979;16(3):283–291.

Foss-Feig JH, Adkinson BD, Ji JL, Yang G, Srihari VH, McPartland JC, Krystal JH, Murray JD, Anticevic A. Searching for cross-diagnostic convergence: neural mechanisms governing

excitation and inhibition balance in schizophrenia and autism spectrum disorders. Biological psychiatry. 2017 May 15;81(10):848-61. https://doi.org/10.1016/j.biopsych.2017.03.005

Freeman WJ. Origin, structure, and role of background EEG activity. Part 4: Neural frame simulation. Clinical Neurophysiology. 2006 Mar 1;117(3):572-89. https://doi.org/10.1016/j.clinph.2005.10.025

Furrer M, Jaramillo V, Volk C, Ringli M, Aellen R, Wehrle FM, Pugin F, Kurth S, Brandeis D, Schmid M, Jenni OG. Sleep EEG slow-wave activity in medicated and unmedicated children and adolescents with attention-deficit/hyperactivity disorder. Translational psychiatry. 2019 Nov 28;9(1):324. https://doi.org/10.1038/s41398-019-0659-3

Gao R, Peterson EJ, Voytek B. Inferring synaptic excitation/inhibition balance from field potentials. Neuroimage. 2017;158: 70–78. https://doi.org/10.1016/j.neuroimage.2017.06.078

Gerster M, Waterstraat G, Litvak V, Lehnertz K, Schnitzler A, Florin E, Curio G, Nikulin V. Separating neural oscillations from aperiodic 1/f activity: challenges and recommendations. Neuroinformatics. 2022 Oct;20(4):991-1012. https://doi.org/10.1007/s12021-022-09581-8

Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going?. Neuron. 2010 Sep 9;67(5):728-34.

Goard M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. Nature Neuroscience. 2009; 12:1444–49. https://doi.org/10.1038/nn.2402

Grice JW, Medellin E, Jones I, Horváth S, McDaniel H, O'lansen C, Baker M. Persons as effect sizes. Advances in Methods and Practices in Psychological Science. 2020 Dec;3(4):443-55. https://doi.org/10.1177/2515245920922982

He BJ, Zempel JM, Snyder AZ, Raichle ME. The temporal structures and functional significance of scale-free brain activity. Neuron. 2010 May 13;66(3):353-69. https://doi.org/10.1016/j.neuron.2010.04.020

He BJ. Scale-free brain activity: past, present, and future. Trends in Cognitive Sciences. 2014 Sep 1;18(9):480-7. http://dx.doi.org/10.1016/j.tics.2014.04.003

Helson P, Lundqvist D, Svenningsson P, Vinding MC, Kumar A. Cortex-wide topography of 1/f-exponent in Parkinson's disease. bioRxiv. 2023:2023-01. https://doi.org/10.1101/2023.01.19.524792

Höhn C, Hahn MA, Lendner JD, Hoedlmoser K. Spectral slope and neural complexity as robust markers of task demand and brain state during sleep and wakefulness. *bioRxiv.* 2022 Sep 10:2022-09. https://doi.org/10.1101/2022.09.10.507390

Horváth CG, Szalárdy O, Ujma PP, Simor P, Gombos F, Kovács I, Dresler M, Bódizs R. Overnight dynamics in scale-free and oscillatory spectral parameters of NREM sleep EEG. Scientific Reports 2022, 12: 18409 https://doi.org/10.1038/s41598-022-23033-y

Ince RA, Kay JW, Schyns PG. Within-participant statistics for cognitive science. Trends in Cognitive Sciences. 2022 Jun 13. https://doi.org/10.1016/j.tics.2022.05.008

Jafarzadeh Esfahani M, Weber FD, Boon M, Anthes S, Almazova T, van Hal M, Keuren Y, Heuvelmans C, Simo E, Bovy L, Adelhofer N, ter Avest MM, Perslev M, ter Horst R, Harous C, Sundelin T, Axelsson J, Dresler M. Validation of the sleep EEG headband ZMax. *bioRxiv.* https://doi.org/10.1101/2023.08.18.553744

Janowsky D, Davis J, El-Yousef MK, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. The Lancet. 1972 Sep 23;300(7778):632-5. https://doi.org/10.1016/S0140-6736(72)93021-8

Jaramillo V, Volk C, Maric A, Furrer M, Fattinger S, Kurth S, Lustenberger C, Huber R. Characterization of overnight slow-wave slope changes across development in an age-, amplitude-, and region-dependent manner. Sleep. 2020 Sep;43(9):zsaa038. https://doi.org/10.1093/sleep/zsaa038

Jenni OG, Carskadon MA. Spectral analysis of the sleep electroencephalogram during adolescence. Sleep. 2004 Jun 1;27(4):774-83. https://doi.org/10.1093/sleep/27.4.774

Kurth S, Ringli M, LeBourgeois MK, Geiger A, Buchmann A, Jenni OG, Huber R. Mapping the electrophysiological marker of sleep depth reveals skill maturation in children and adolescents. Neuroimage. 2012 Nov 1;63(2):959-65. https://doi.org/10.1016/j.neuroimage.2012.03.053

Lansey JC. 2020. Power Law, Exponential and Logarithmic Fit, MATLAB Central File Exchange. https://www.mathworks.com/matlabcentral/fileexchange/29545-power-law-exponential-and-logarithmic-fit

Le Bon O, Staner L, Rivelli SK, Hoffmann G, Pelc I, Linkowski P. Correlations using the NREM-REM sleep cycle frequency support distinct regulation mechanisms for REM and NREM sleep. Journal of Applied Physiology. 2002 Jul 1;93(1):141-6. https://doi.org/10.1152/japplphysiol.00917.2001

Le Bon O. Relationships between REM and NREM in the NREM-REM sleep cycle: a review on competing concepts. Sleep medicine. 2020 Jun 1;70:6-16. https://doi.org/10.1016/j.sleep.2020.02.004

Lendner JD, Helfrich RF, Mander BA, Romundstad L, Lin JJ, Walker MP, Larsson PG, Knight RT. An electrophysiological marker of arousal level in humans. Elife. 2020;9. https://doi.org/10.7554/eLife.55092

Merica H, Fortune RD. The neuronal transition probability (NTP) model for the dynamic progression of non-REM sleep EEG: the role of the suprachiasmatic nucleus. PloS one. 2011 Aug 19;6(8):e23593. https://doi.org/10.1371/journal.pone.0023593

Milstein J, Mormann F, Fried I, Koch C. Neuronal shot noise and Brownian 1/f2 behavior in the local field potential. PloS one. 2009 Feb 3;4(2):e4338. https://doi.org/10.1371/journal.pone.0004338

Miskovic V, MacDonald KJ, Rhodes LJ, Cote KA. Changes in EEG multiscale entropy and power-law frequency scaling during the human sleep cycle. Human Brain Mapping. 2019 Feb 1;40(2):538-51. https://doi.org/10.1002/hbm.24393

Monk TH. Aging human circadian rhythms: conventional wisdom may not always be right. Journal of biological rhythms. 2005 Aug;20(4):366-74. https://doi.org/10.1177/0748730405277378

Nir Y, Tononi G. Dreaming and the brain: from phenomenology to neurophysiology. Trends in cognitive sciences. 2010 Feb 1;14(2):88-100. https://doi.org/10.1016/j.tics.2009.12.001

Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Computational intelligence and neuroscience. 2011 Oct;2011. https://doi:org/10.1155/2011/156869

Osorio-Forero A, Foustoukos G, Cardis R, Cherrad N, Devenoges C, Fernandez LM, Luthi A. Locus coeruleus activity fluctuations set a non-reducible timeframe for mammalian NREM-REM sleep cycles. bioRxiv. 2023:2023-05. https://doi.org/10.1101/2023.05.20.541586

Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nature Reviews Neuroscience. 2002 Aug 1;3(8):591-605. https://doi.org/10.1038/nrn895

Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: state of the art. Sleep medicine reviews. 2013 Oct 1;17(5):377-90. 10.1016/j.smrv.2012.11.001

Pathania A, Euler MJ, Clark M, Cowan RL, Duff K, Lohse KR. Resting EEG spectral slopes are associated with age-related differences in information processing speed. Biological Psychology. 2022 Feb 1;168:108261. https://doi.org/10.1016/j.biopsycho.2022.108261

Pillai JA, Leverenz JB. Sleep and neurodegeneration: a critical appraisal. Chest. 2017 https://doi.org/10.1016/j.chest.2017.01.002

Randler C. Chronotype in children and adolescents. Somnologie 2016; 20:166–71. https://doi.org/10.1007/s11818-016-0073-5

Rosenblum Y, Bovy L, Weber FD, Steiger A, Zeising M, Dresler M. Increased aperiodic neural activity during sleep in major depressive disorder. Biological Psychiatry Global Open Science. 2023 Oct 1;3(4):1021-9. https://doi.org/10.1016/j.bpsgos.2022.10.001

Rosenblum Y, Pereira M, Stange O, Weber FD, Bovy L, Tzioridou S, Lancini E, Neville DA, Klein N, de Wolff T, Stritzke M, Kersten I, Uhr M, Claassen JAHR, Steiger A, Verbeek MM, Dresler M. Divergent associations of slow-wave sleep vs. REM sleep with plasma amyloid-beta. 2023. BioRxiv. https://doi.org/10.1101/2023.06.02.543111

Rosenblum Y, Shiner T, Bregman N, Giladi N, Maidan I, Fahoum F, Mirelman A. Decreased aperiodic neural activity in Parkinson's disease and dementia with Lewy bodies. Journal of Neurology. 2023 May 3:1-2. https://doi.org/10.1007/s00415-023-11728-9

Rosenblum Y, Weber FD, Rak M, Zavecz Z, Kunath N, Breitenstein B, Zeising M, Steiger A, Dresler M. Sustained polyphasic sleep restriction abolishes human growth hormone release. Sleep, 2023, zsad321, https://doi.org/10.1093/sleep/zsad321

Scammell TE. Narcolepsy. New England Journal of Medicine. 2015 Dec 31;373(27):2654-62. https://doi.org/10.1056/NEJMra1500587

Schneider B, Szalárdy O, Ujma PP, Simor P, Gombos F, Kovács I, Dresler M, Bódizs R. Scale-free and oscillatory spectral measures of sleep stages in humans. Frontiers in Neuroinformatics 2022, 16: 989262 https://doi.org/10.3389/fninf.2022.989262

Schwarz JF, Åkerstedt T, Lindberg E, Gruber G, Fischer H, Theorell-Haglöw J. Age affects sleep microstructure more than sleep macrostructure. Journal of sleep research. 2017 Jun;26(3):277-87. 10.1111/jsr.12478

Simor P, Bogdány T, Peigneux P. Predictive coding, multisensory integration, and attentional control: A multicomponent framework for lucid dreaming. Proceedings of the National

Academy of Sciences. 2022 Nov 1;119(44):e2123418119. https://doi.org/10.1073/pnas.2123418119

Simor P, Peigneux P, Bódizs R. Sleep and dreaming in the light of reactive and predictive homeostasis. Neuroscience & Biobehavioral Reviews. 2023 Feb 17:105104. https://doi.org/10.1016/j.neubiorev.2023.105104

Tarokh L, Carskadon MA, Achermann P. Dissipation of sleep pressure is stable across adolescence. Neuroscience. 2012 Aug 2;216:167-77. https://doi.org/10.1016/j.neuroscience.2012.04.055

Vinding M, Eriksson A, Manting C, Waldthaler J, Ferreira D, Ingvar M, Svenningsson P, Lundqvist D. Changes in non-oscillatory features of the cortical sensorimotor rhythm in Parkinson's disease across age. https://doi.org/10.21203/rs.3.rs-1699006/v1

Vogel GW, Buffenstein A, Minter K, Hennessey A. Drug effects on REM sleep and on endogenous depression. Neuroscience & Biobehavioral Reviews. 1990 Mar 1;14(1):49-63. https://doi.org/10.1016/S0149-7634(05)80159-9

Volk C, Jaramillo V, Studler M, Furrer M, Tuura RL, Huber R. Diurnal changes in human brain glutamate+ glutamine levels in the course of development and their relationship to sleep. Neuroimage. 2019 Aug 1;196:269-75. https://doi.org/10.1016/j.neuroimage.2019.04.040

Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. Biological Psychiatry. 2015 Jun 15;77(12):1089-97. https://doi.org/10.1016/j.biopsych.2015.04.016

Wen H, Liu Z. Separating fractal and oscillatory components in the power spectrum of neurophysiological signal. Brain topography. 2016 Jan;29(1):13-26.

Wichniak A, Wierzbicka A, Jernajczyk W. Sleep as a biomarker for depression. International review of psychiatry. 2013 Oct 1;25(5):632-45. https://doi.org/10.3109/09540261.2013.812067