Figures and figure supplements

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

Yevgenia Rosenblum *et al.*

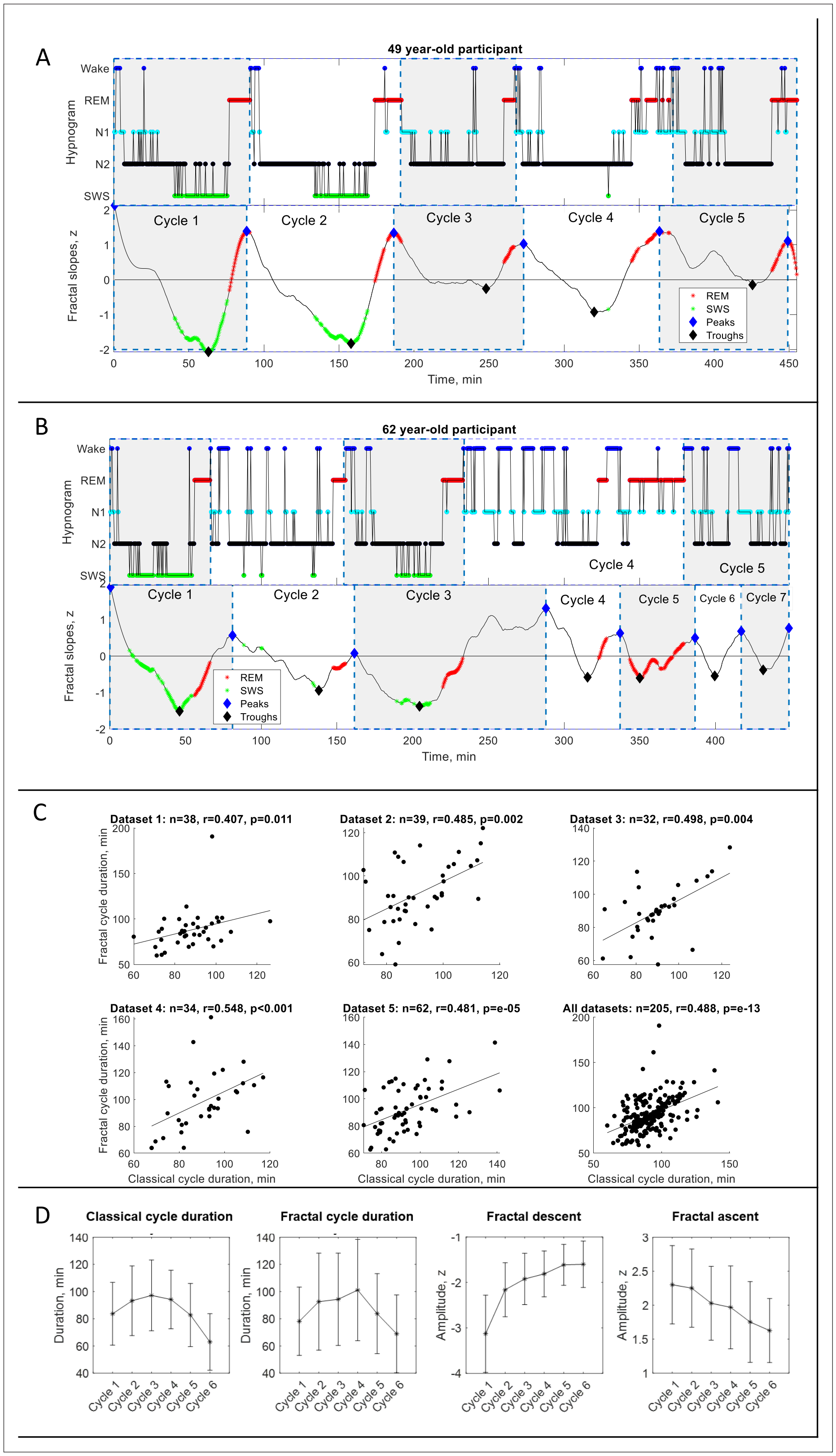

Figure 1. Fractal cycles in healthy adults. (**A – B**) Individual fractal and classical sleep cycles. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top) observed in two different participants. The duration of the fractal cycle is a time interval between two successive peaks (blue diamonds). (**A**) S15 from Dataset 3 shows a one-to-one match between fractal cycles defined by the algorithm and classical

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(non-REM – REM) cycles defined by the hypnogram. (**B**) In S22 from dataset 5, 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) are expected to result in more peaks and, consequently, more fractal cycles, that is a shorter cycle duration. This is one of the possible explanations for the correlation between the fractal cycle duration and age (shown in ***Figure 1—figure supplement 4A***). Time series of the fractal slopes and corresponding hypnograms for all participants are reported in Supplementary PowerPoint File shared on https://osf.io/gxzyd. SWS – slow-wave sleep, REM – rapid eye movement. (**C**) 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. (**D**) 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.

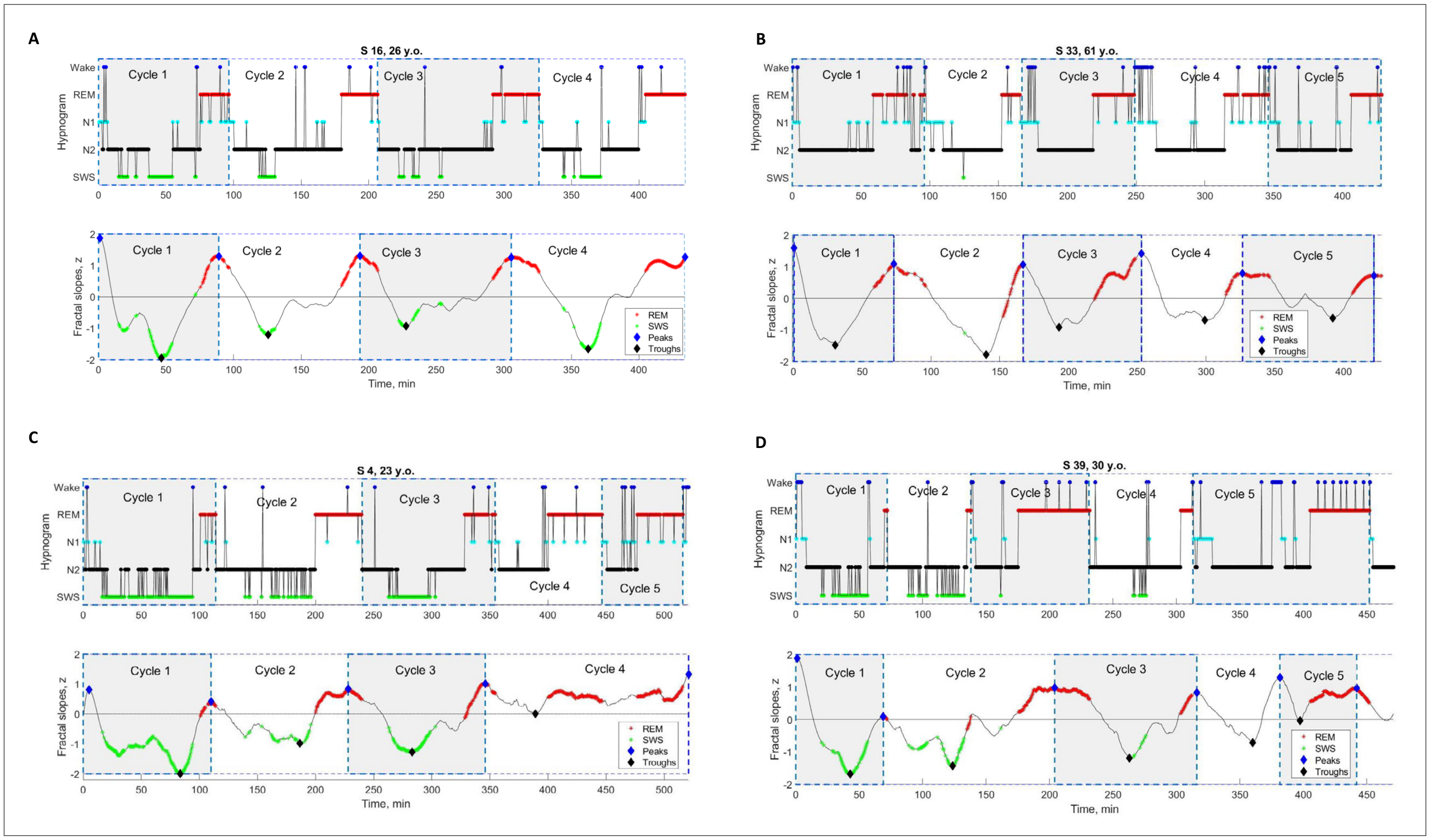

Figure 1—figure supplement 1. Individual fractal and classical sleep cycles in healthy adults. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top). The duration of the fractal cycle is an interval of time between two successive peaks (blue diamonds) defined with Matlab's function *findpeaks* with the minimum peak distance of 40 min and minimum peak prominence of 0.9 z. Supplementary PowerPoint File shared on https://osf.io/gxzyd presents these time series and hypnograms for all participants. (**A – B**) one-to-one match. In these two participants (from Dataset 3), there is an almost one-to-one match between fractal cycles defined by the algorithm and classical (non-REM – REM) cycles defined by the hypnogram. (**C – D**) algorithm's misses. Two participants from Dataset. 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. SWS – slow-wave sleep, REM – rapid eye movement sleep.

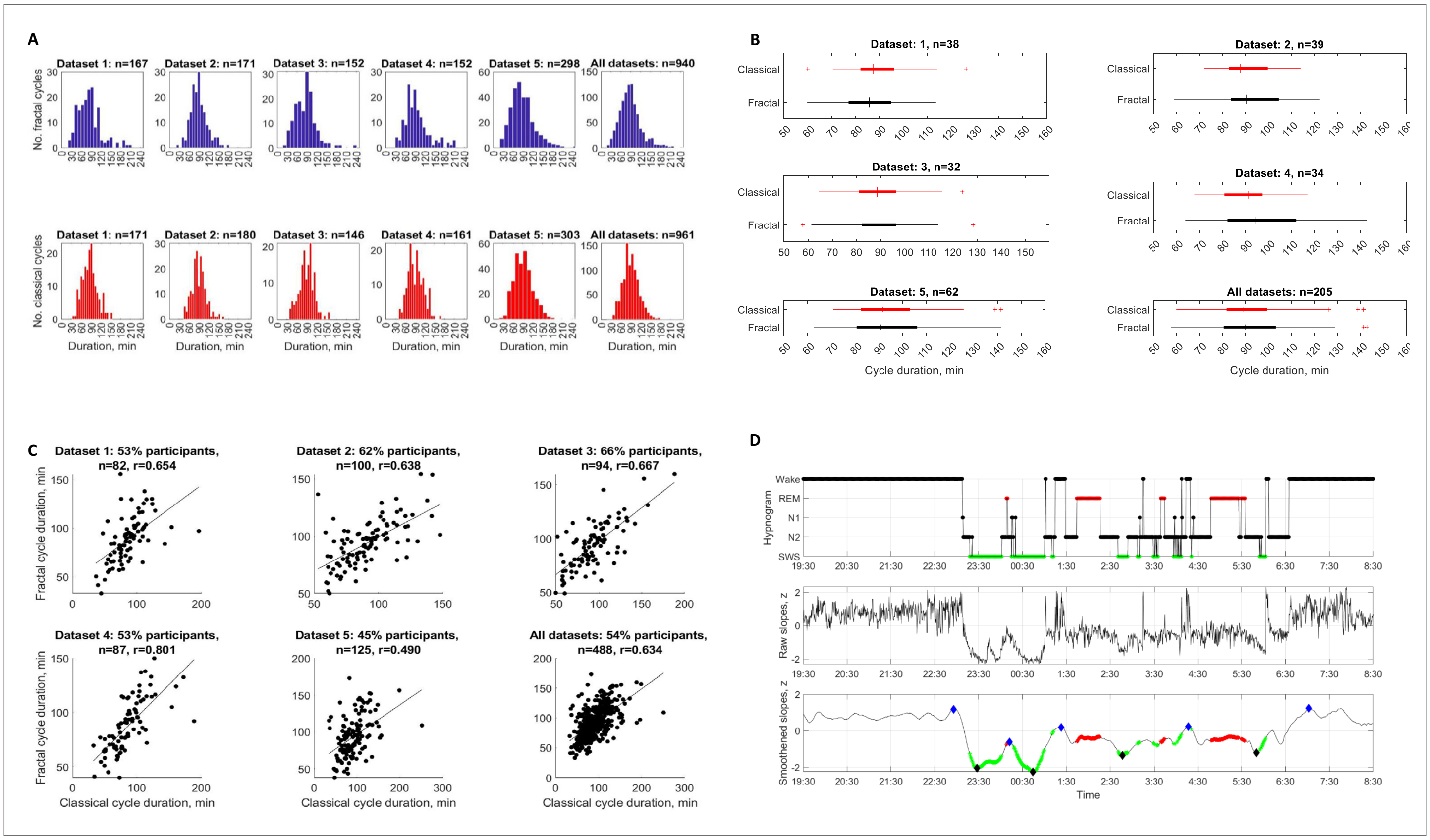

Figure 1—figure supplement 2. Fractal and classical cycles: distributions, means, correlations and an individual example. (**A**) Frequency distribution of fractal and classical cycle durations. The individual fractal (top) and classical (bottom) cycles are counted (**n**) for each dataset separately 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. (**B**) Box plots of fractal and classical cycle durations. 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. (**C**) A subset of healthy adults with a one-to-one match between fractal and classical cycles durations (correlations). 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 < 10^{-9}, r – Spearman's correlation coefficient. (**D**) Individual fractal time series across 13 hr. Time series of raw (middle) and smoothed z-normalized fractal slopes (bottom) as well as the corresponding hypnograms (top) in a 25-year-old healthy male. In addition to sleep-related fractal activity, this figure shows fractal activity during 3 hr before the sleep onset and 2 hr after awakening. The graph shows that fractal cycles are not observed during wake, being specific to sleep. This participant does not come from the datasets depicted in the current study (where no recordings >8 h were available). The study, EEG device and preprocessing are described in ***Rosenblum et al., 2024b***. EEG power was averaged over F4, C4, and O2 electrodes, differentiated into its components, z-scored and smoothed as described in Methods of the current paper. The duration of the fractal cycle is a time interval between two successive peaks (blue diamonds). SWS – slow-wave sleep (green dots), REM – rapid eye movement sleep (red dots).

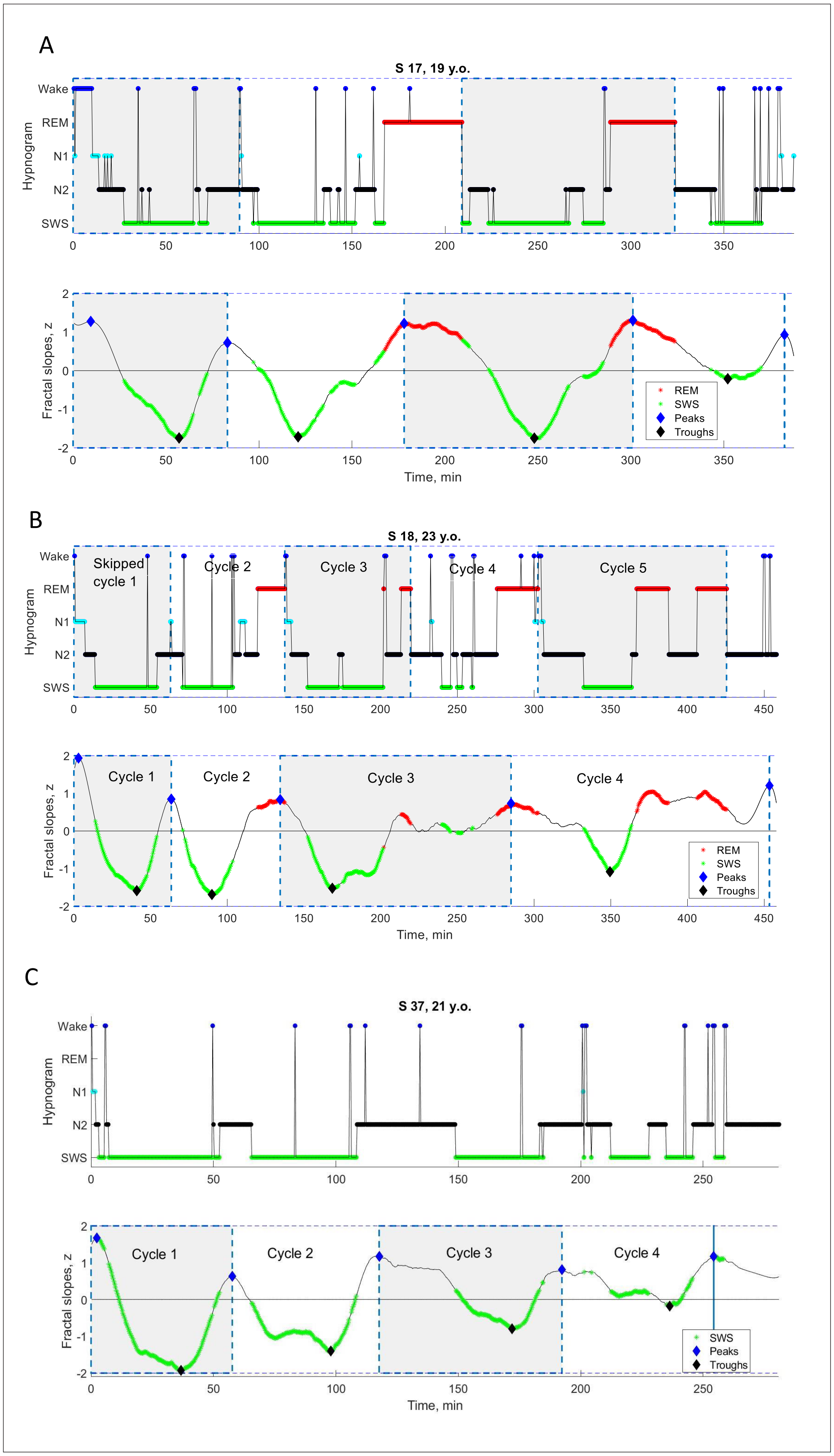

Figure 1—figure supplement 3. Individual cycles with skipped REM sleep. Time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top) observed in three young healthy participants (from Dataset 4). Hypnograms show skipped first cycles (as well as the rest of the classical cycles). (**A**) 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

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observed. We divided the long 209 min cycle into two cycles, the 90 min skipped cycle and the 119 min normal cycle. (**B**) 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 min cycle into two cycles, the 63 min skipped cycle and the 75 min 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. (**C**) S37's hypnogram shows that she has no REM sleep at all, that is all her cycles are the 'skipped' ones. Based on this, S37 was even excluded from the formal analysis. This example is presented here to illustrate that the fractal cycle algorithm is sensitive enough in detecting sleep cycles even in the absence of REM sleep. SWS – slow-wave sleep, REM – rapid eye movement sleep.

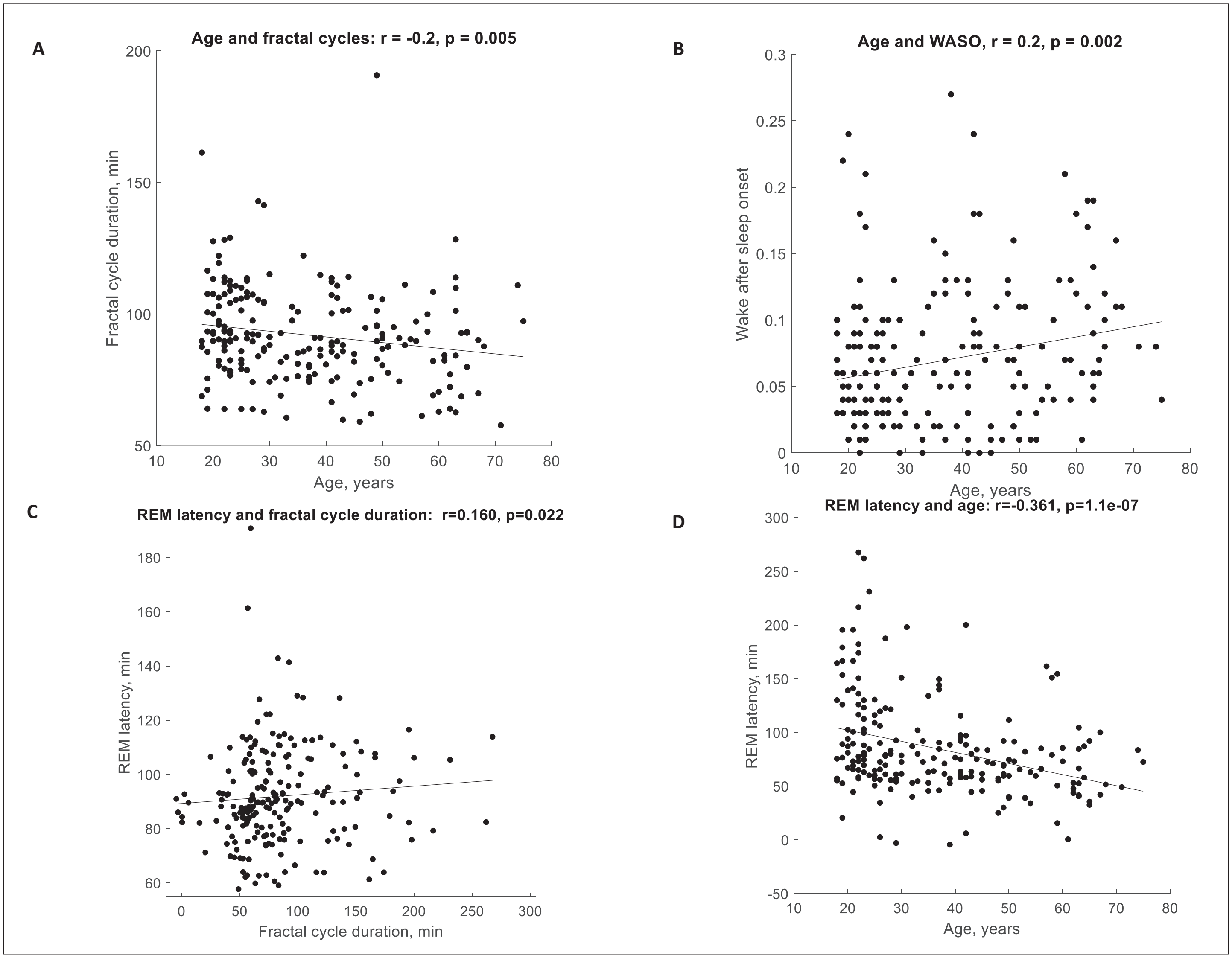

Figure 1—figure supplement 4. Correlations. (**A**) Fractal cycle duration negatively correlates with the age of healthy participants. (**B**) The WASO proportion positively correlates with the age of healthy participants. The partial correlations between the fractal cycle duration and age adjusted for WASO and REM latency remained significant. (**C**) Fractal cycle duration positively correlates with REM latency of the healthy participants. (**D**) 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.

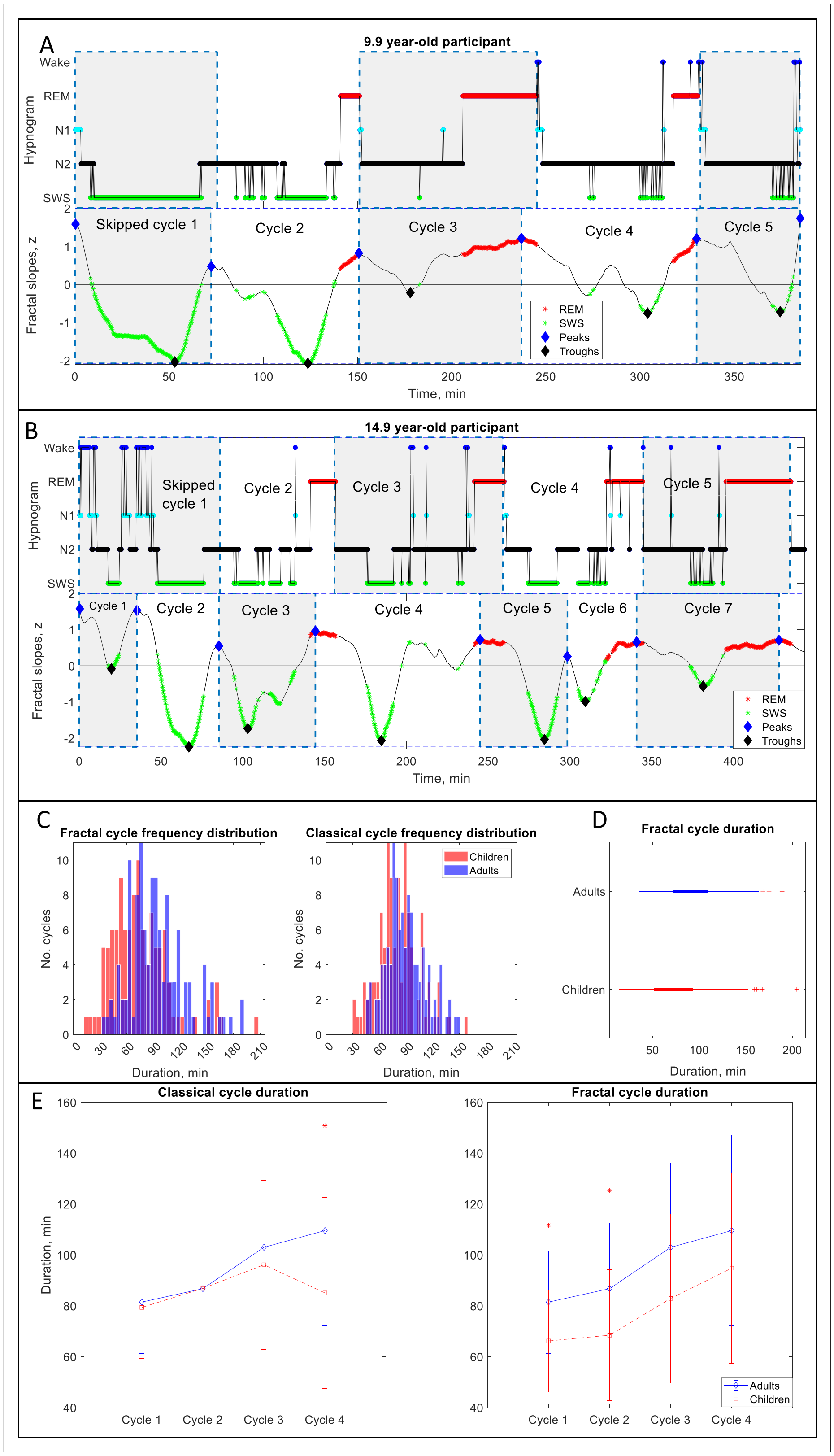

Figure 2. Fractal cycles in children and adolescents. (**A, B**) Individual cycles: time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top). The duration of the fractal cycle is a time interval between two successive peaks (blue diamonds) defined with the Matlab function *findpeaks* with a minimum peak distance of 20 min and minimum peak prominence of 0.9 z. SWS – slow-wave sleep, REM – rapid eye

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movement sleep. (**A**) In this 9.9-year-old participant (from Dataset 6), we split the first 150-min-long classical cycle into two cycles according to the definitions of a 'skipped' cycle presented in Materials and methods. The fractal cycle algorithm successfully detected this skipped cycle. (**B**) This 14.9-year-old participant has a 156-min-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. (**C**) 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. (**D**) 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. (**E**) Overnight dynamics: cycle-to-cycle dynamics show that the first and the second fractal cycles are shorter in the pediatric compared to control group, * marks a statistically significant difference between the groups.

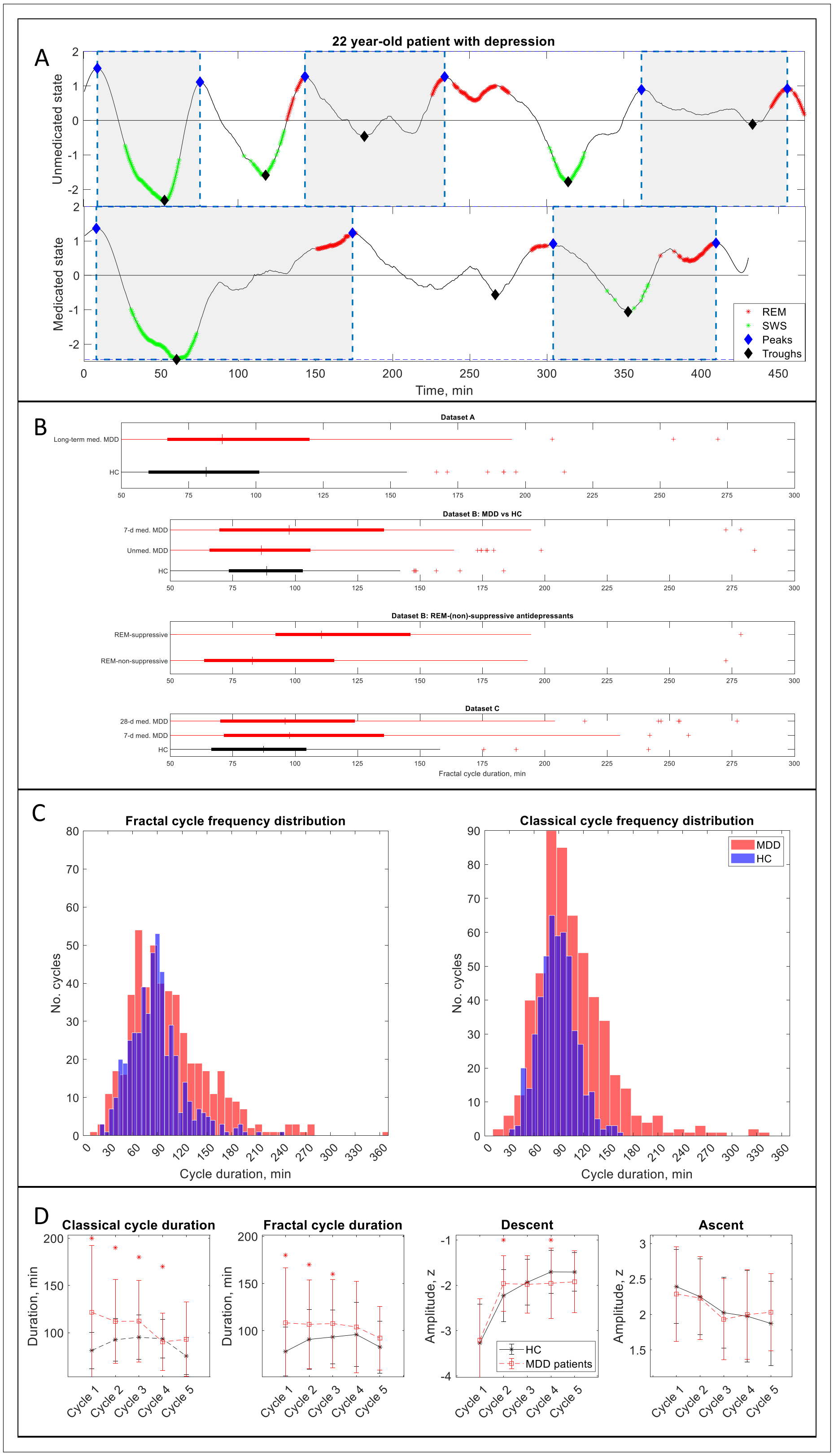

Figure 3. Fractal cycles in MDD. (**A**) Individual fractal cycles: time series of smoothed z-normalized fractal slopes observed in a 22 y.o. MDD patient (Dataset B) in their unmedicated (top) and 7-day medicated (bottom) states. Peaks (blue diamonds) are defined with the Matlab function *findpeaks* with the minimum peak distance of 20 min and minimum peak prominence of 0.9 z. Fractal cycles duration (defined as an interval of time between two

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successive peaks) is longer in the medicated compared to unmedicated states, reflecting shallower fluctuations of fractal (aperiodic) activity. Two additional patients are shown in ***Figure 3—figure supplement 1***. (**B**) 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). (**C**) Frequency distribution: individual fractal and classical cycles pooled from three MDD datasets (**A – C**) are counted separately for medicated MDD patients and HC. (**D**) 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. MDD – major depressive disorder, HC – healthy controls, unmed. – unmedicated, med. – medicated, SWS – slow-wave sleep, REM – rapid eye movement.

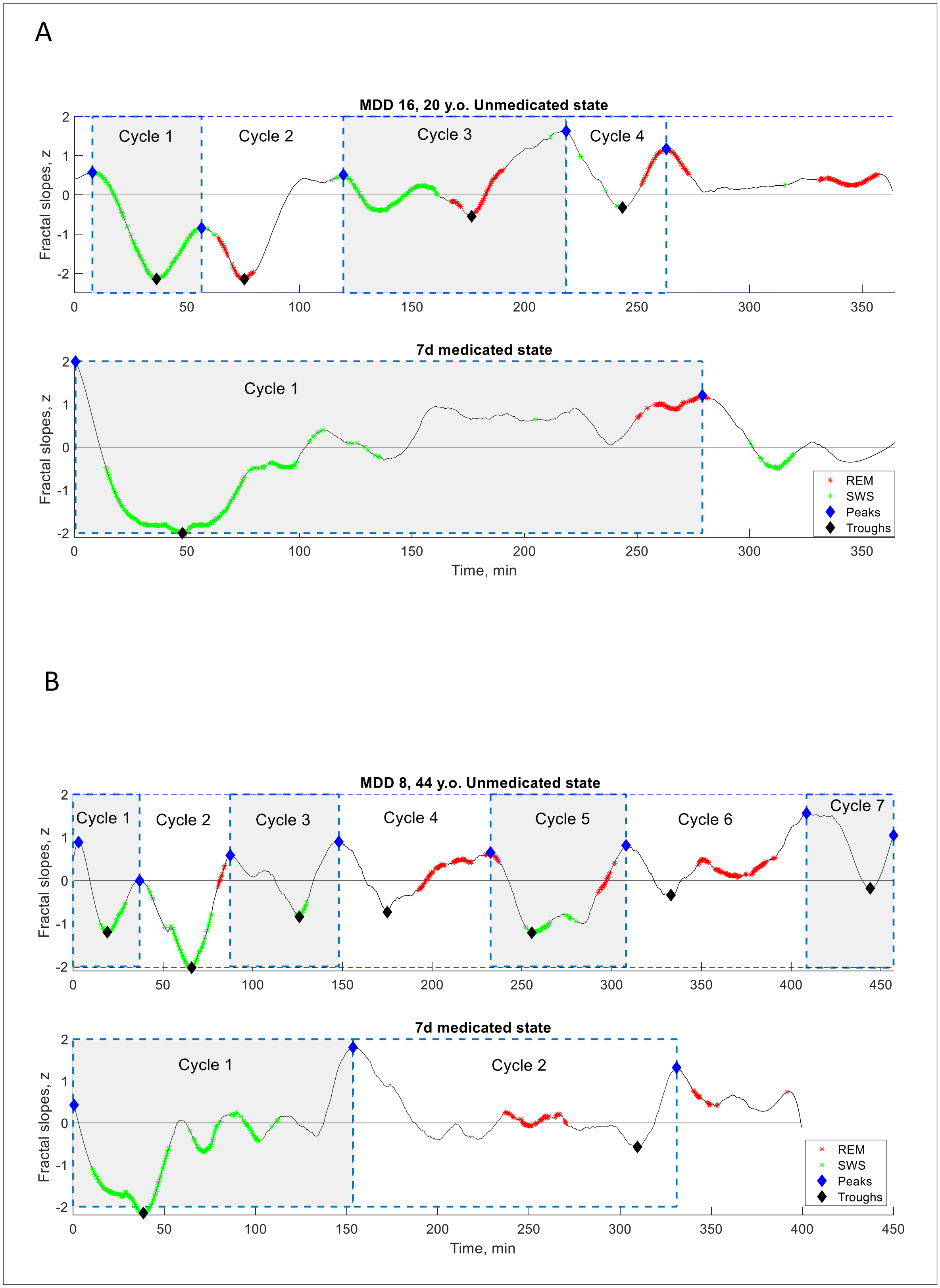

Figure 3—figure supplement 1. Individual fractal cycles in MDD patients. Time series of smoothed z-normalized fractal slopes observed in two additional MDD patients (Dataset B) in their unmedicated (top) and 7-day medicated (bottom) states. Fractal cycles duration (defined as an interval of time between two successive peaks, blue diamonds) 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 sleep.

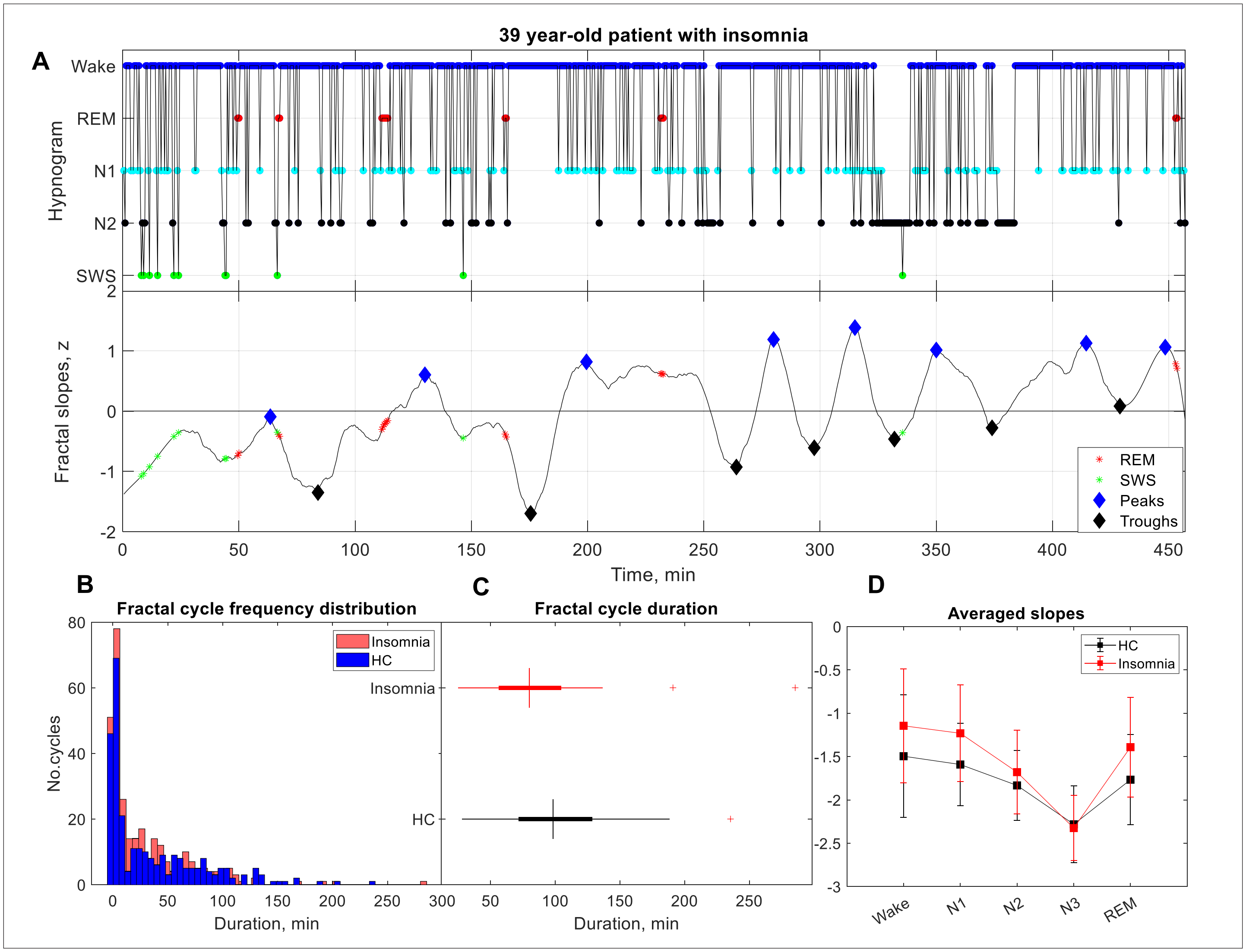

Figure 3—figure supplement 2. Fractal cycles in patients with insomnia. (**A**) Individual example: time series of smoothed z-normalized fractal slopes (bottom) and corresponding hypnograms (top). The duration of the fractal cycle is a time interval between two successive peaks (blue diamonds) defined with Matlab's function *findpeaks* with a minimum peak distance of 20 min and minimum peak prominence of 0.9 z. SWS – slow-wave sleep, REM – rapid eye movement sleep. (**B**) Histograms: The frequency distribution of fractal cycle durations in patients with insomnia compared to controls. Kolmogorov-Smirnov's test rejected the assumption that cycle duration comes from a standard normal distribution. (**C**) 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. Patients with insomnia show shorter fractal cycle duration compared to controls. (**D**) Averaged slopes: The slopes of the frontal fractal spectral power components in the 1–18 Hz range are averaged over each sleep stage as defined by the hypnogram. N3 is characterized by the steepest (most negative slopes) spectral decay compared to all other sleep stages in line with the existing literature. Patients present with flatter slopes compared to controls in all sleep stages confirming previous findings (***Andrillon et al., 2020***).

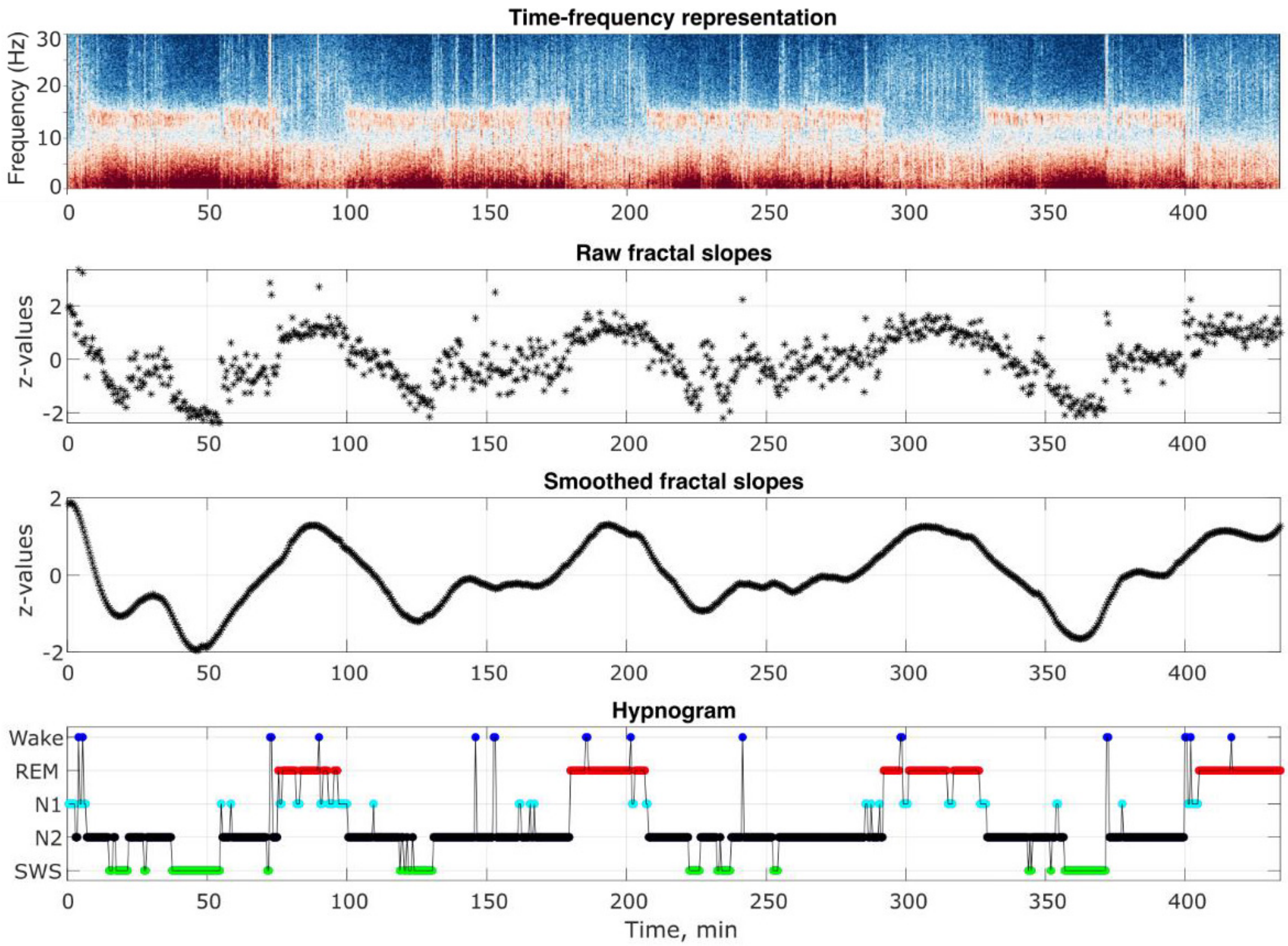

Figure 4. Analysis output examples. Outputs of some of the analysis steps in an example healthy 26-year-old individual. From top to bottom: time-frequency representation of the total spectral power, raw and smoothed time series of the fractal slopes and hypnogram. Frontal spectral power and its slopes were calculated in the 0.3–30 Hz range for each 30 s of sleep.

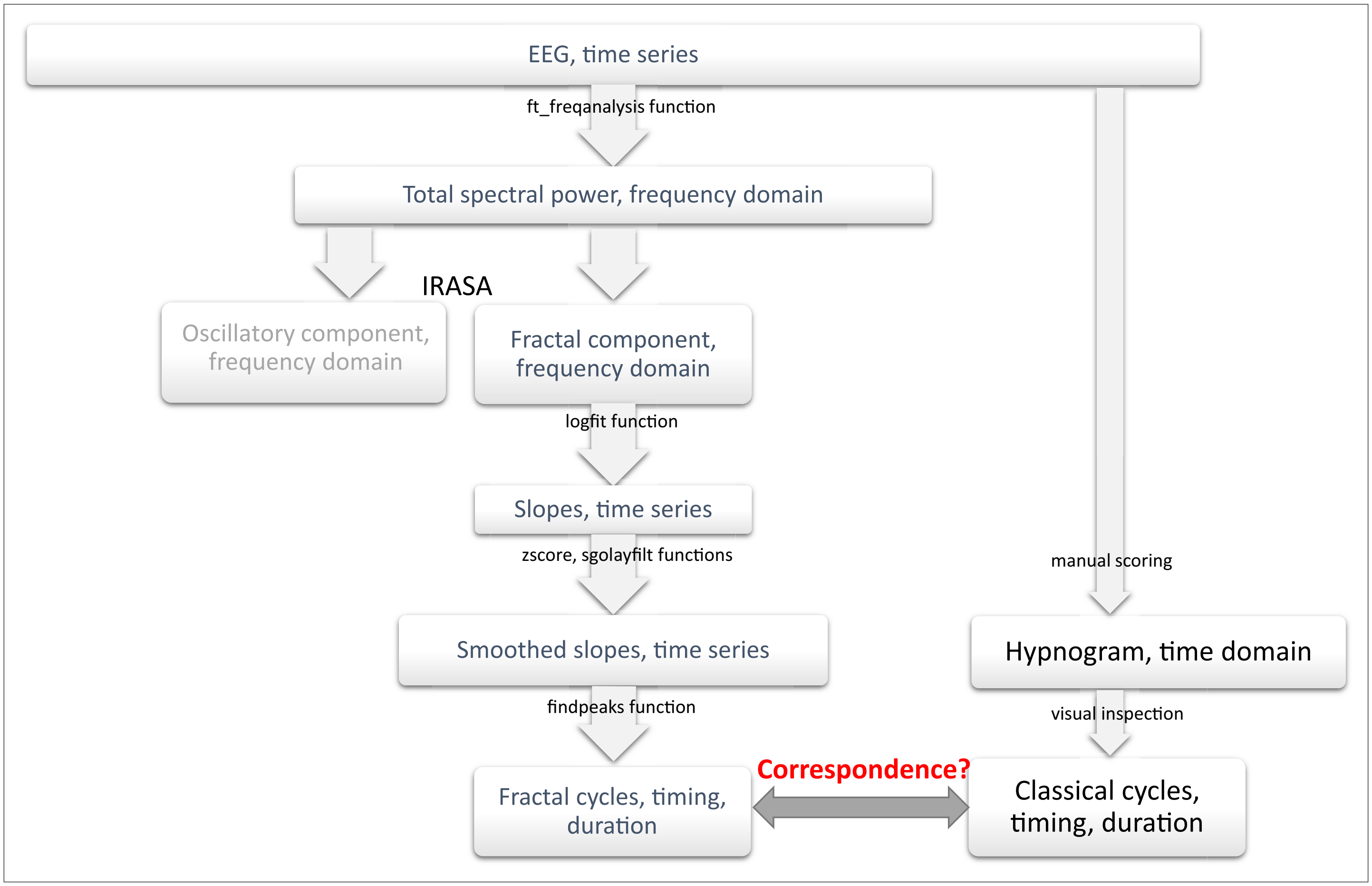

Figure 4—figure supplement 1. Analysis flowchart. IRASA – Irregularly Resampled Auto-Spectral Analysis, *sgolayfilt* – Savitzky-Golay filter.

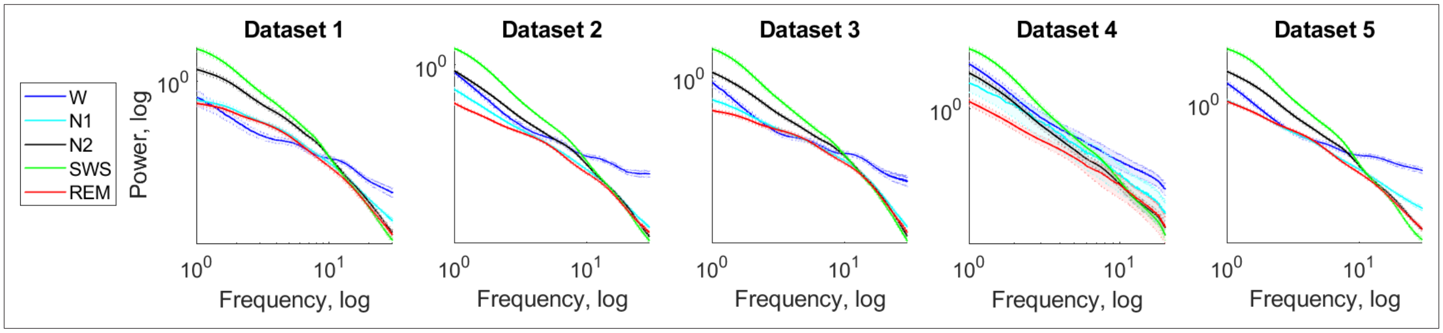

Figure 4—figure supplement 2. Fractal power component. Fractal (aperiodic) power components averaged over each sleep stage separately over all participants of a given dataset are plotted as a function of frequency in the log-log space. Shading indicates standard errors. Slow-wave (green) and REM (red) sleep stages show the steepest and the flattest spectral decay, respectively in all datasets. For comparison, wake after sleep onset (blue) with the flattest decay in the higher frequency band is also shown.

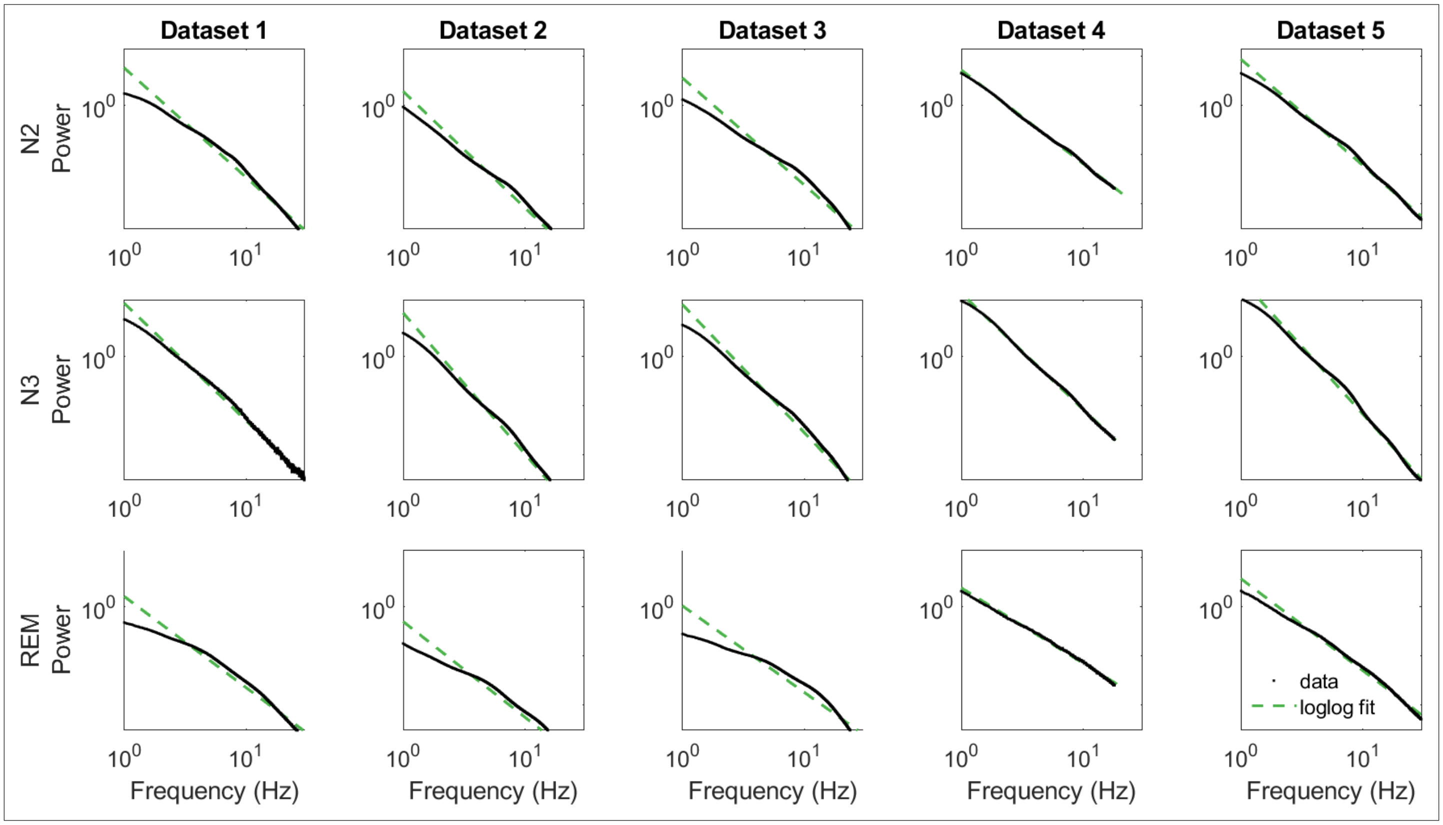

Figure 4—figure supplement 3. Log-log fit of data. N – non-REM sleep, N3 – slow-wave sleep, REM – rapid eye movement sleep. Of note, in this study, we did not average spectral power/its slope over sleep stages; these graphs are shown to put our study in a broader context of the studies that looked at spectral power averaged over sleep stages for visualization only.

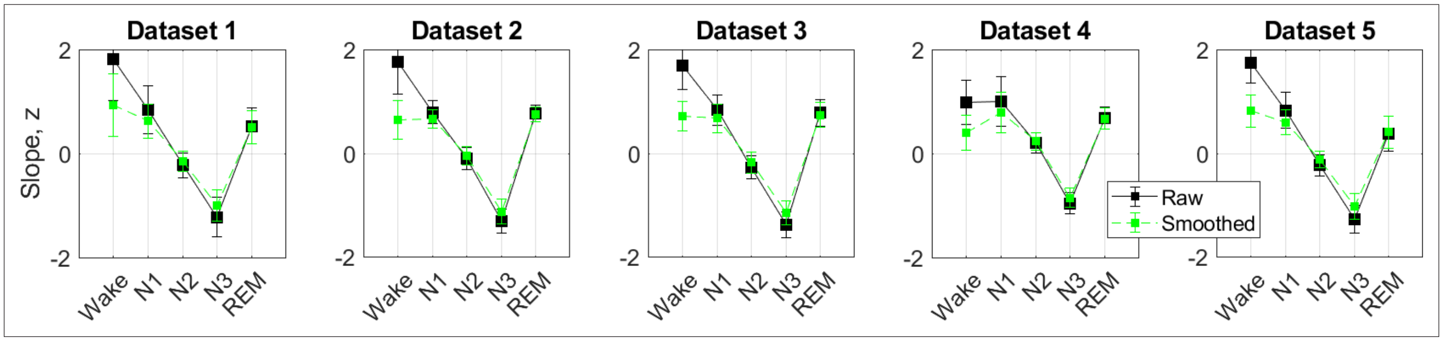

Figure 4—figure supplement 4. 0.3–30 Hz z-normalized slopes. The slopes of the frontal fractal spectral power components in the 0.3–30 Hz range are averaged over each sleep stage as defined by the hypnogram and z-normalized (black squares). For the analysis of the fractal cycles reported in the main text, fractal slopes were smoothened using the Savitzky-Golay filter (green squares). N3 is characterized by the steepest (most negative slopes) spectral decay compared to all other sleep stages in line with the existing literature.

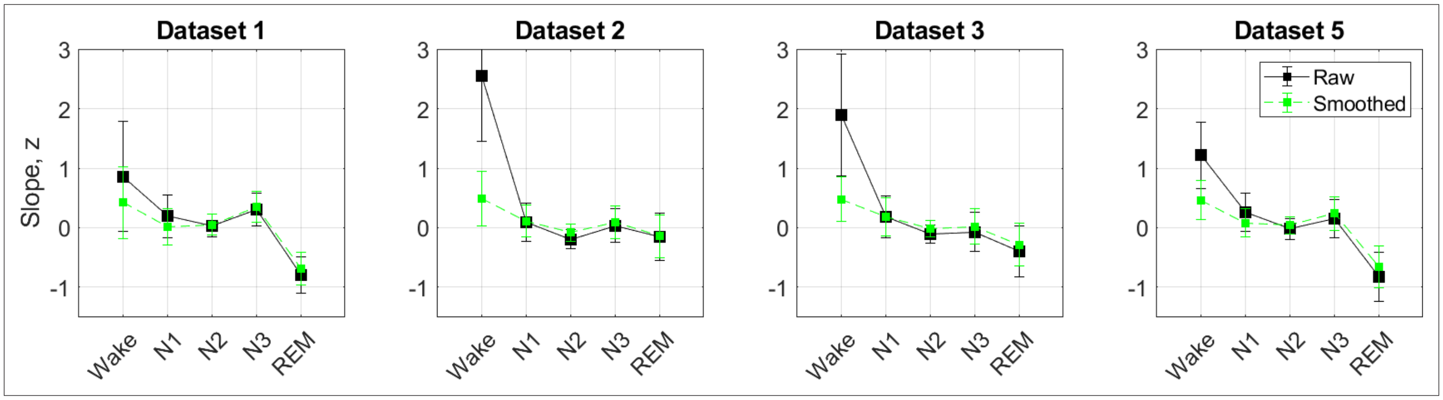

Figure 4—figure supplement 5. 30–48 Hz z-normalized slopes. The slopes of the aperiodic (fractal) spectral power component in the 30–48 Hz range are averaged over each sleep stage as defined by the hypnogram and z-normalized (black squares). Green squares show fractal slopes smoothened with the Savitzky-Golay filter. 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 analyses. Note: During recording, Dataset 4 was filtered in the 0.2–35 Hz range and therefore, it was excluded from this subanalysis.

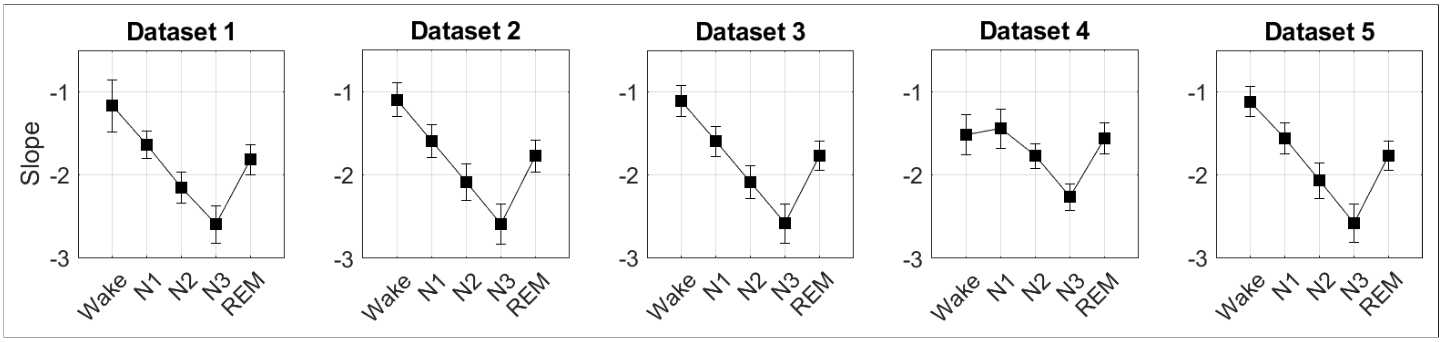

Figure 4—figure supplement 6. 0.3–30 Hz raw slopes. Given that raw slope values contain valuable information per se (***Bódizs et al., 2024***), we also report raw slope values (before z-scoring). Note: Dataset 4 was filtered in the 0.3–18 Hz range due to low-pass filtering during the recording.

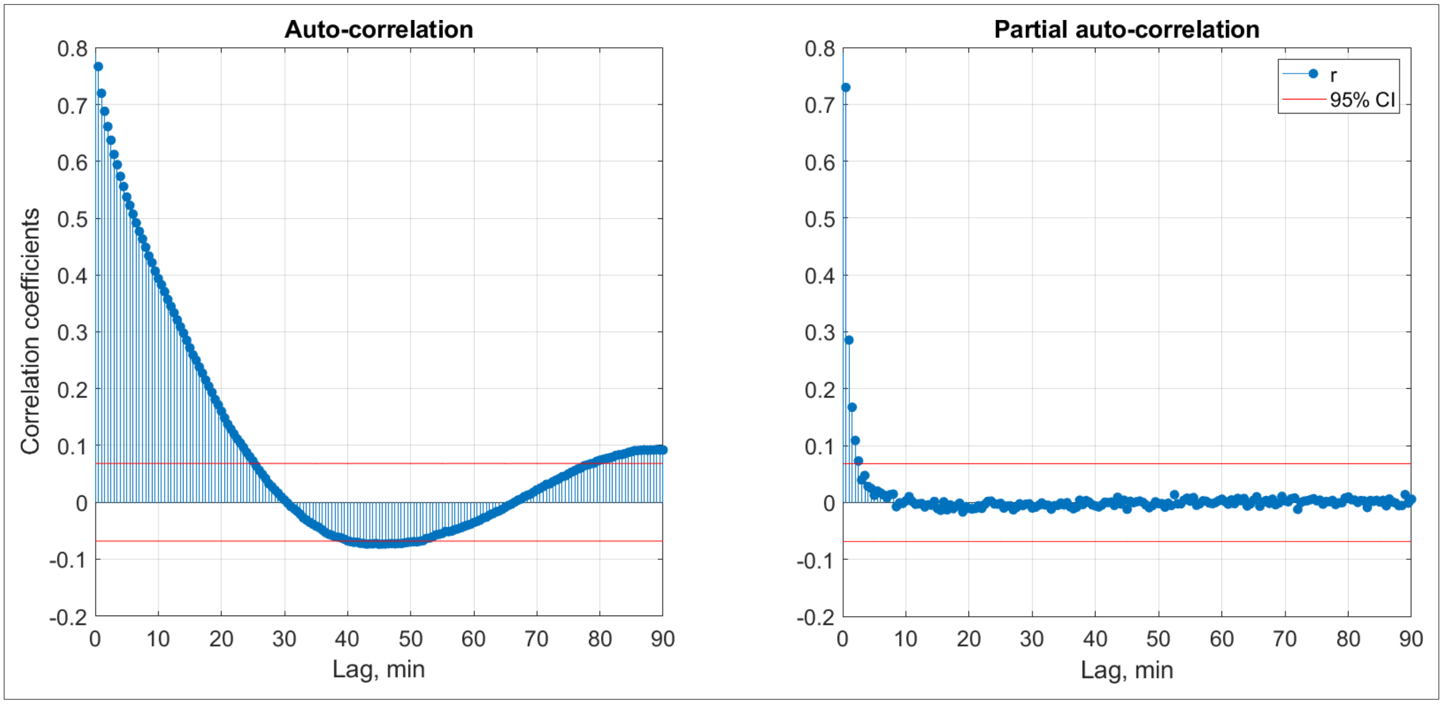

Figure 4—figure supplement 7. Autocorrelation (*left*) and partial autocorrelation (*right*) of the time series of the fractal slopes averaged over each 30 s of sleep show the correlation of this time series with a delayed version of itself as a function of time lag. Red horizontal lines indicate approximate 95% probability limits for a purely random process. Correlation coefficients were calculated separately for each participant and then averaged over the pooled dataset (n=205).

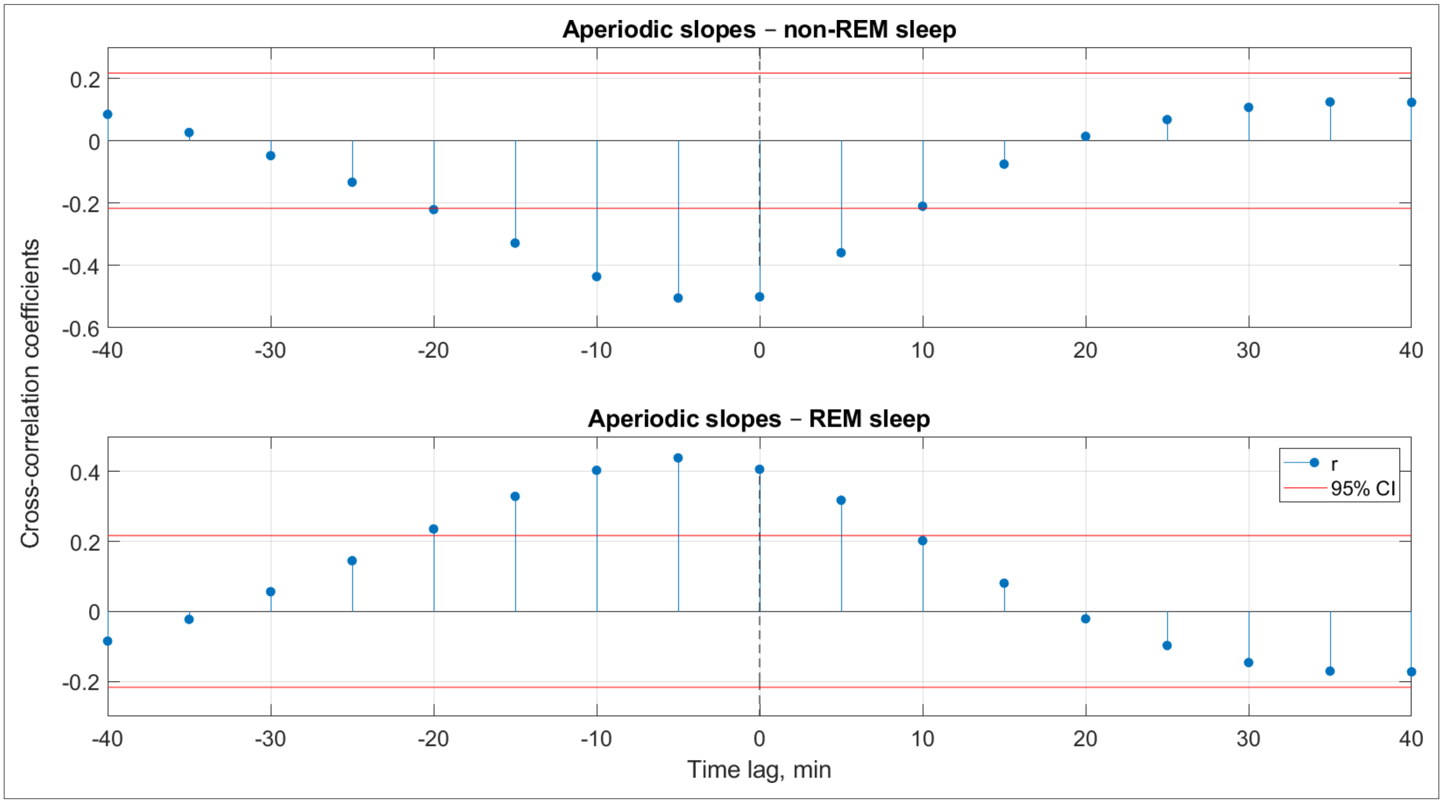

Figure 4—figure supplement 8. Cross-correlations. Cross-correlations between the time series of fractal slopes on the one side and the proportion of non-REM (top) or REM sleep (bottom) per 5 min on the other side. Cross-correlations were calculated for each participant individually, then correlation coefficients were averaged over all healthy adults (n=205). Negative and positive lags mean that fractal slope time series are leading and lagging, respectively. Here, the shape of the cross-correlation function does not allow one to decide which time series is leading and which one is lagging here. The horizontal red lines mark the CI of 95%, the absolute values above these lines indicate statistical significance (r > |0.22|). REM – rapid eye movement sleep, CI – confidence interval.

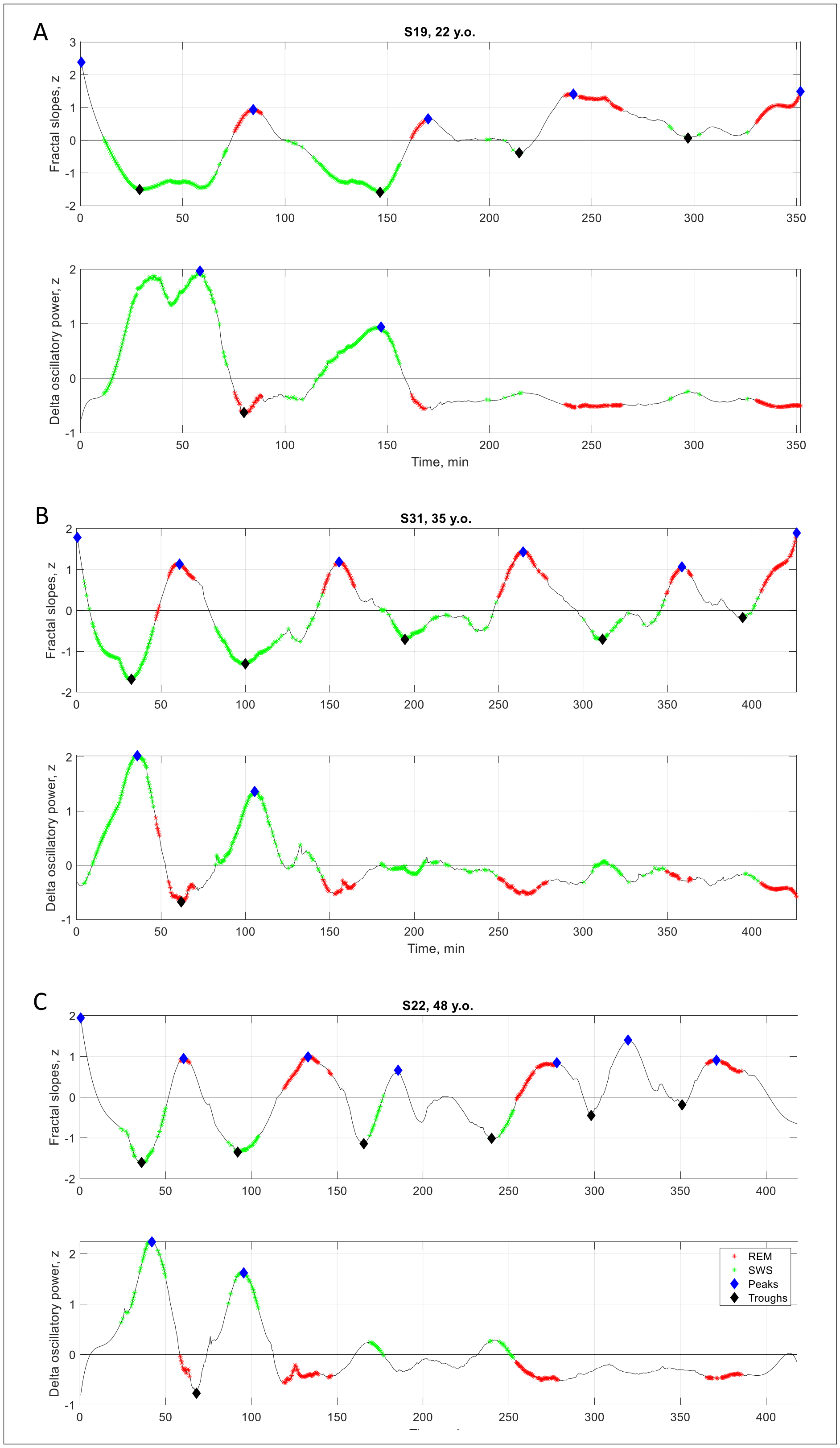

Figure 4—figure supplement 9. Individual fractal *vs.* SWA time series. Time series of smoothed z-normalized fractal slopes (top) and SWA/delta (1–4 Hz) oscillatory power (bottom) observed in three healthy adults (from Dataset 3). SWS – slow-wave sleep, SWA – slow-wave activity, REM – rapid eye movement sleep.