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Increased aperiodic neural activity during sleep in major depressive disorder

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Abstract

Background. In major depressive disorder (MDD), patients often express subjective sleep complaints while polysomnographic studies report only subtle alterations of the electroencephalographic (EEG) signal. We hypothesize that differentiating the signal into its oscillatory and aperiodic components may bring new insights into our understanding of sleep abnormalities in MDD. Specifically, we investigate aperiodic neural activity during sleep and its relationships with the sleep architecture, depression severity, and responsivity to antidepressant treatment.
Methods. Polysomnography was recorded in 38 MDD patients (in unmedicated and 7-day medicated states) and 38 age-matched healthy controls (n=76). Aperiodic power component was calculated using the Irregularly Resampled Auto-Spectral Analysis. Depression severity was assessed with the Hamilton Depression Rating Scale. We replicated the analysis using two independently collected datasets of medicated patients and controls (n=60 and n=80).

Results. Unmedicated patients showed flatter aperiodic slopes compared to controls during non-REM 2 sleep (p=0.009). Medicated patients showed flatter aperiodic slopes compared to their later medicated state (p-values<0.001) and controls during all sleep stages (p-values<0.03). In medicated patients, flatter aperiodic slopes during non-REM sleep were linked to the higher proportion of non-REM 1, lower proportion of REM, delayed onset of non-REM-3 and REM, and shorter total sleep time.

Conclusion. Flatter slopes of aperiodic EEG power may reflect noisier neural activity due to increased excitation-to-inhibition balance, representing a new disease-relevant feature of sleep in MDD.

Keywords: major depressive disorder, impaired sleep, aperiodic power, excitation-to-inhibition ratio, antidepressants, neural noise.

Short title: A periodic neural activity in major depressive disorder
I. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder characterized by at least two weeks of pervasive low mood, anhedonia, inappropriate guilt, and feelings of worthlessness (1). In 2017, MDD affected ~2% of the world population (2). The percentage of people who are affected at one point in their life varies from 7% to 21%, reflecting the fact that MDD is a serious public health problem (2). Besides abnormalities of mood and affect, MDD patients often have sleep complaints, including insomnia (in ~60%) or hypersomnia (in ~15%), as well as fatigue, excessive daytime sleepiness, and lack of concentration while awake (3). Broad evidence suggests that disturbances of sleep-wake rhythms and circadian time-keeping system underlie the pathophysiology of depression (4). Understanding the mechanisms of these alterations might bring new insights into the understanding of MDD.

Intriguingly, whereas some polysomnographic studies confirm subjective sleep complaints of the patients by reporting decreased slow-wave and delta amplitudes, higher spindle amplitude, lower spindle density, and a more dispersed slow-wave-spindle coupling, others suggest that oscillatory changes in MDD might be more subtle (5, 6). One of the possible explanations for the divergent oscillatory findings is the confounding effect of aperiodic (i.e., non-oscillatory, scale-free) activity (7-9). For that reason, recently, it has been recommended to differentiate the total electroencephalographic (EEG) spectral power into its oscillatory and aperiodic components in order to "avoid misrepresentation and misinterpretation of the data" while studying oscillations (7-9). In addition, exploring aperiodic activity is important per se as it is a distinct type of brain dynamics with its own functional significance and rich information content able to provide a window into diverse neural processes (8-10).
Currently, aperiodic activity receives increasing attention with reports on aperiodic changes associated with sleep phases, tasks, age, and disease (7-16). Notably, it has been shown that the slope of the aperiodic component reflects the ratio between excitatory and inhibitory currents in the brain (10, 15, 16), while the height of the spectra is related to neural spiking rates (8, 10). Besides this, a steeper aperiodic spectrum can also reflect greater synchronization while a flatter spectrum can indicate reduced synchronization (i.e., greater neural noise; 14). In view of the crucial role of the proper balance between neural excitation and inhibition (E/I) for healthy cognition, behavior (17), and sleep, aperiodic activity seems to be a promising tool for investigating MDD with its cholinergic, monoaminergic (18, 19), glutamatergic (20), and GABAergic imbalance (21, 22). In MDD, the E/I ratio could be further affected by prescribed antidepressants.

In view of this background, here, we explore aperiodic activity during sleep in MDD and its relationships with the sleep architecture, depression severity, and responsivity to antidepressant treatment. This study has an exploratory nature with no a priori hypothesis on the direction of aperiodic changes.

2. Methods and Materials

Participants

We retrospectively analyzed polysomnographic recordings from a previous study conducted at the Max Planck Institute of Psychiatry, Munich, Germany (6). The sample consisted of 40 patients.
with MDD and 40 healthy controls individually matched by age (±2 years of tolerance) and gender (Table 1). None of the patients was treated with sedative antidepressants.

Exclusion criteria included suicidality, shift working, transmeridian flights in the preceding three months, drug or alcohol dependence, professional piano skills, professional typewriting skills, sleep disorders, pregnancy, and a history of severe physical disorders. Subjects who received long-acting medication before the beginning of the experiment were excluded if the treatment was not stopped in time to ensure a complete wash-out (e.g., antipsychotics, fluoxetine). Due to technical failure in the EEG data of two medicated patients, all paired analyses were matched on the remaining full datasets (n=38 per group).

To confirm the results, we replicated the analyses using two independently collected datasets of short and long-term medicated MDD patients (Supplementary Material-5). All studies were approved by the Ethics committee of the University of Munich. All participants gave written informed consent.

**Questionnaires**

Depression severity of patients was measured with the Hamilton Depression Rating Scale (HAM-D) at baseline ("unmedicated") and 7 days after the commencement of antidepressant treatment ("medicated"). A higher score reflects higher depression severity. In Supplementary Material-4, we also report the Pittsburgh Sleep Quality Index, which was available in a subset of the patients.

**Polysomnography**

All participants slept in the sleep laboratory, and all had an adaptation night before the examination night. For the EEG of the examination night, 118 Ag/AgCl electrodes were applied using an
Easycap 128Ch-BrainCap (EasyCap GmbH, Herrsching, Germany). Polysomnography was recorded (sampling rate of 200 Hz), stored, and digitized following the 10-5 system (23) with a JE-209A amplifier (Neurofax Software, Nihon Kohden Europe GmbH, Rosbach, Germany) with a common-mode rejection ratio of ≥ 110 dB and with impedances below 10 kOhm, including EEG (filtered at 0.016 Hz high pass only, -6 dB/octave), electrooculography, mental/submental electromyography with a ground electrode attached at the forehead. During the recording, the EEG was referenced to the average of the AFF5H and AFF1H, which were predefined by the hardware setup. For the offline analysis, the data was re-referenced to the average of all electrodes.

Polysomnography of the patients was recorded at two timepoints: when unmedicated and when 7-day medicated. Sleep was scored by independent experts according to the AASM standards (24). We analyzed separately all sleep stages and the wakefulness occurring after sleep onset (WASO). The epochs scored as the “wake” before the sleep onset and after morning awakening were excluded from the analysis as they were not available for all participants. 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. The rejection percentage is reported in Supplementary Table S6.1.

In Supplementary Material S-3, we also report morning resting-state EEG measured in a subset of participants to explore whether the observed effects are specific to sleep.

Spectral power

Total EEG power was differentiated into its aperiodic (fractal) and oscillatory components using the Irregularly Resampled Auto-Spectral Analysis (25). A MATLAB implementation of the algorithm was adapted from the Fieldtrip website (http://www.fieldtriptoolbox.org/example/irasa).
Specifically, we used the `ft_freqanalysis` function with the `cfg.method='irasa'` for each 30 s of sleep, corresponding to the conventionally defined sleep epochs. The function was called twice, with the `cfg.output='fractal'` and `cfg.output='original'` for the total power and its aperiodic component, respectively. The aperiodic component was transformed to log-log coordinates by standard least squares regression, where the slope of the line was calculated as the power-law exponent estimation.

Power was averaged over each sleep stage as defined by the hypnogram over five topographical areas: 1) frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8, F9, F10); 2) central (Cz, C1, C2, C3, C4, C5, C6); 3) parietal (Pz, P1, P2, P3, P4, P5, P6, P7, P8, P9, P10); 4) occipital (Oz, O1, O2); 5) temporal (T7, T8).

The signal was filtered in the 0.2–48Hz frequency band. In Supplementary Material-1, we also analyze low (2–20Hz) and high (30–48Hz) bands to control for a possible distortion of the linear fit by excluding low frequencies with strong oscillatory activity (15) and for the reliable discrimination between wakefulness and REM sleep, respectively (16).

In Supplementary Material-2, we report the analysis of the oscillatory component to explore whether the effect is specific to aperiodic activity.

**Statistical analysis**

To analyze aperiodic slopes, we used five ANCOVAs for each sleep stage separately with the five-level "brain area" as within-subject factor and two-level "study group" as between-subjects factor to compare 1) unmedicated patients and controls; 2) the same patients when 7-day medicated and
controls. Even though we matched the participants' age individually, given that at the group level the age ranged from 19 to 54 years, we added to the analysis the "age" factor as a covariate. In view of between-group differences in the proportions of sleep stages (Table 1), when appropriate (namely, for WASO and REM), we added to the ANCOVAs the proportion of a given sleep stage in each study group as an additional covariate. We performed five additional ANOVAs for each sleep stage separately to compare unmedicated and 7-day medicated states of the patients using the "state" as the within-subject factor.

The Benjamini-Hochberg's adjustment was applied to control for multiple comparisons (5 tests reflecting the number of sleep stages) with a false discovery rate set at 0.05 and the α-level set in the 0.01–0.05 range. For all ANOVAs/ANCOVAs we applied Greenhouse-Geisser correction since Mauchly's test revealed that the sphericity assumption was violated (ε<0.75, p<0.05). The assumptions of normality and homogeneity of variance were tested using the Q-Q plot and Levene's homogeneity test, respectively.

Then, we performed post hoc analysis to compare each pair of groups for each area and sleep stage separately. We used the two-tailed Student's unpaired t-test to compare patients to controls and paired t-test to compare the unmedicated and medicated states of the patients. Effect sizes were calculated with Cohen's d.

To study the effect of the antidepressant treatment on aperiodic activity we stratified the patients by 1) antidepressant class; 2) REM-suppressive vs REM-non-suppressive antidepressants as reported in Table 2. Then, we performed 25 non-parametric Mann-Whitney U two-tailed tests for each sleep stage and area separately, since after this stratification the samples were too small to
perform ANOVA. Benjamini-Hochberg’s adjustment for 25 tests (5 stages by 5 areas) was applied with the α-level set in the 0.002–0.050 range.

The diagnostic accuracy of the frontal aperiodic slopes was defined using the area under the Receiver Operating Characteristic curve (AUC). Pearson’s correlations were used to assess associations between the frontal aperiodic slopes on one side and 1) features of sleep architecture; 2) HAM-D scores of the participants at baseline and 7-day on the other side. SPSS software (version 25; SPSS, Inc) was used for all statistical analyses.

3. Results

The demographic, clinical, and sleep characteristics of the participants are reported in Table 1. Patients in both the unmedicated and medicated states showed increased WASO compared to controls. Medicated patients further showed decreased REM sleep proportion and prolonged REM sleep onset compared to the controls and own unmedicated state.

Aperiodic slopes

Frontal total spectral power and its components for all sleep stages for all study groups are shown in Fig.1. The results are presented in Table 3 and Fig.2. Unmedicated patients showed flatter slopes compared to controls during N2 (p=0.009) in all areas and during N3 sleep (p=0.04) in the frontal and temporal areas with medium effect sizes.
Medicated patients showed flatter slopes compared to controls during N1, N2, N3, and REM sleep in all areas with medium effect sizes. These findings were replicated in two independent datasets (Supplementary Material-5).

Patients in the medicated state showed flatter slopes compared to the own unmedicated state with large effect size during REM sleep and with small effect size during N3. Likewise, the medicated state showed flatter slopes during N1 and N2 in the frontal, central, and temporal areas with small effect sizes compared to the unmedicated state (Fig.2, Table 3).

Aperiodic slopes did not correlate with depression severity (HAM-D scores) neither at baseline nor at 7-day assessments.

**ROC analysis**

Frontal slopes measured during N1, N2, N3, and REM sleep discriminated both between the unmedicated state of the patients and controls (AUC=0.66–0.74, all p-values<0.02) as well as between the medicated state of the patients and controls (AUC=0.74–0.76, all p-values<0.001).

**Medication effect**

The demographic and clinical characteristics of the subgroups of patients stratified by the medication class are reported in Table 2. The results are presented in Fig.3 and Supplementary Material-5 (Table S5.5).
The patients who took REM-suppressive antidepressants showed flatter slopes compared to patients who took REM-non-suppressive antidepressants during N1 (F=13.9, p=0.001), N2 (F=42.8, p<0.001), N3 (F=21.9, p<0.001), and REM sleep (F=10.4, p=0.003) with large effect sizes (d-values=0.6–2.2).

The patients who took REM-suppressive SNRIs showed flatter slopes during N2, N3, and REM sleep with large to huge effect sizes compared to the patients who took non-SNRIs (p-values<0.001–0.026, d-values=0.9–2.8). These patients also showed flatter slopes compared to the patients who took non-SNRIs REM-suppressive antidepressants (p-values=0.005–0.019, d-values=1.5–1.7), such as SSRIs (p-values=0.009–0.028, d-values=1.3–1.8) during REM sleep with very large effect sizes. However, these findings did not pass the correction for multiple comparisons. Aperiodic activity was comparable among patients who took SSRIs, TCAs, or NDRIs compared to their pooled controls.

Aperiodic slopes and sleep architecture

Correlations between aperiodic slopes and sleep architecture are reported in Table 4. In unmedicated patients, flatter aperiodic slopes during N1 were associated with the delayed onset of N3. In medicated patients, flatter aperiodic slopes during non-REM sleep were linked to the higher proportion of N1, lower proportion of REM, delayed onset of N3 and REM, and shorter total sleep time. In controls, flatter aperiodic slopes during N3 sleep were associated with the higher proportion of WASO and lower proportion of REM sleep. Some of these findings were replicated in an independent dataset (Supplementary Material-5, Table S5.2).
The reported in the Results alterations were specific to sleep and were not observed during the morning resting state (Supplementary Material-3).

4. Discussion

To the best of our knowledge, this is the first study that examines sleep-related aperiodic activity in MDD and its relationships with the sleep architecture, depression severity, and responsivity to antidepressant treatment. We found that unmedicated patients show flatter aperiodic slopes during non-REM sleep compared to controls. Patients in the medicated state show flatter aperiodic slopes compared to the own unmedicated state and healthy controls during both non-REM and REM sleep. In medicated patients, flatter aperiodic slopes during non-REM sleep were linked to the lower proportion and delayed onset of REM sleep. We replicated several of our findings in two independently collected datasets of medicated patients. Below we aim at an interpretation of these findings.

The functional significance of aperiodic dynamics is still a mystery with several interpretations suggested so far. For example, aperiodic activity can manifest in the overall firing rate of cortical neurons (9, 15, 26) as measured by local field potentials or EEG. When many neurons fire relatively simultaneously, the power spectrum will decay faster, being relatively stronger in low frequencies and relatively weaker in the higher ones. Mathematically, this will be expressed by a more negative (steeper) slope, which, in turn, reflects a higher power-law exponent. A steeper slope can signify redundancy (11), excessive or insufficient propagation of the signal (27), or
increased dendritic filtering (26). When neurons fire relatively asynchronously, the spectral power is shifted towards higher frequencies and its slope is flatter, reflecting reduced temporal autocorrelations (8), high entropy rate of cortical systems (28), or a noisier neural background (29-31). Following this, flatter aperiodic slopes observed here in unmedicated and medicated MDD patients may reflect noisier neural background activity (31), which in turn can adversely affect sleep and its restorative function.

Adding to this, pharmacological, physiological, and computational studies linked aperiodic activity to the balance between excitatory and inhibitory currents in the brain (15, 16). Specifically, Gao et al. (15) showed that the aperiodic slope in the 30-50Hz range reliably tracked the induction and the recovery from propofol-induced anesthesia in rats and macaques. Similarly, in humans, inhibition was boosted by the propofol administration, and the slope became steeper when inhibition increased (16). Subsequent studies interpreted the l/f exponent as an indicator of E/I balance also for other frequency bands, e.g., 3-55Hz (10), 0.5-35Hz (31), 1-40Hz, 1-20Hz, 20-40Hz (32). In Supplementary Material-1, we analyzed aperiodic activity in the 2-20Hz and 30-48Hz bands and confirmed the broadband (0.2-48Hz) analysis reported in the main text with the exception of the high-band activity, which was comparable in unmedicated patients and controls.

The right balance between neural excitation and inhibition is crucial for optimal signal formation and transmission, synaptic plasticity, neuronal growth, and pruning and, thus, enables flexible behavior and cognition (17). Correspondingly, any perturbations in the E/I balance may lead to brain disease (17). For example, schizophrenia has been associated with a low E/I ratio caused by hypoactive receptors for the excitatory neurotransmitter glutamate (17) and steeper aperiodic slopes compared to controls during rest (33). Analogously, depression might be associated with
E/I perturbations due to its cholinergic-monoaminergic (18, 19), glutamatergic (20), and/or GABAergic imbalance.

Thus, it has been suggested that GABAergic deficit may play a central role in the etiology of MDD, especially in melancholic (21) and treatment-resistant types of depression (22), while targeting the E/I imbalance in depression via enhancing the GABAergic system with antidepressant therapies may contribute to a greater remission rate and reduce the risk of relapse (34). At the cellular level, changes in GABAergic interneurons affect the regulation of excitatory signals from and onto pyramidal neurons (35), the primary contributors to the EEG signal. Following this literature, flatter aperiodic slopes observed here during sleep in unmedicated and medicated patients may reflect a shift in the E/I ratio in favor of excitation due to cellular alterations of the GABAergic, glutamatergic, and cholinergic-monoaminergic systems. Nevertheless, it should be stressed that thus far, there is no evidence that altered aperiodic dynamics can be used as readouts of cholinergic, monoaminergic, glutamatergic, and GABAergic imbalance. Moreover, whereas some authors suggest that the aperiodic slope is an indicator of E/I balance (10, 15, 16), others state that currently, the relationship between aperiodic slopes and E/I balance remains a hypothesis to be further validated (7). In addition, when aiming to link aperiodic slopes and E/I balance, one should keep in mind that aperiodic 1/f-like processes are very ubiquitous in nature and are not limited to neural activity (7, 10, 11).

Of special interest was the effect of antidepressants: we found that during all sleep stages, medicated patients showed flatter slopes compared to controls. We replicated this association using two independently collected datasets of short and long-term medicated patients (Supplementary Material-5). In addition, we found that the medicated state showed flatter slopes compared to the own unmedicated state. In line with our findings, a recent study in healthy females has reported
that one week of intake of the SSRI escitalopram induces a flattening of aperiodic slopes during
rest in favor of excitation (36).

Furthermore, we found that in 7-day medicated patients, flatter aperiodic slopes during non-REM
sleep correlated with such alterations in sleep architecture as a higher proportion of non-REM
stage 1, a lower proportion of REM, delayed onset of non-REM stage 3 and REM sleep, and shorter
total sleep time. In the literature, these alterations in sleep architecture are often interpreted as
impaired sleep (37). Specifically, MDD patients have been reported to show prolonged sleep
latency, increased WASO, early morning awakening, reduced slow-wave sleep, shortened latency
and increased amount of REM sleep (38). Here, unmedicated MDD patients have shown increased
WASO while other sleep architecture features were comparable to those measured in controls. The
same patients in the medicated state showed increased WASO, decreased REM sleep proportion
and prolonged REM sleep onset.

Delayed onset and reduced amount of REM sleep are well-known aftereffects of almost all
antidepressants (38). Notably, we replicated the association between flatter aperiodic slopes during
non-REM sleep and a decreased proportion of REM sleep and delayed REM sleep onset using an
independent dataset of 7-day medicated patients (Supplementary Material 5, Table S5.2). This link
is in line with the previous proposition that some antidepressants (for example, such SNRI as
venlafaxine) may impair sleep due to their activating effects (39). Furthermore, the observed
association suggests that aperiodic slopes flattening seen in medicated MDD patients is a potential
readout of altered sleep architecture and impaired sleep known in this disorder. Nevertheless,
further studies are needed to test this possibility.
Whereas our findings bring new insights about the association between aperiodic activity, sleep architecture, and antidepressants, they do not advance the current understanding of the treatment response (or lack thereof) as changes in aperiodic activity did not correlate with clinical improvement (as assessed by the HAM-D). It is possible that other depression scales (that were not available in this study) would be more sensitive in detecting the hypothesized association between depression severity and aperiodic activity. Given that a deeper understanding of the antidepressants' effects on sleep is crucial for successful treatment, future large-scale longitudinal research is required to reveal whether aperiodic activity can serve as a marker for predicting individual cortical responsivity to different antidepressants.

Besides their clinical importance, our findings are also essential from the methodological point of view as they confirm the importance of a recent recommendation to differentiate the total spectral power to its components in order "to avoid misrepresentation and misinterpretation of the data" (8, 9). Namely, we observed comparable total (i.e., non-differentiated to its components) spectral power (analyzed in 6) but different oscillatory and aperiodic components in unmedicated MDD patients and controls (Fig.1).

Finally, here, aperiodic alterations were observed during sleep but not during WASO suggesting their specificity to sleep. Nevertheless, it should be kept in mind that the wake EEG is more variable and prone to artifacts than sleep EEG; therefore, the performed analysis might have not enough statistical power to detect between-group differences. Interestingly, in unmedicated patients, the morning resting state EEG showed steeper low-band and flatter high-band slopes compared to controls, while broadband slopes were comparable in both groups. This preliminary finding, however, requires further validation due to the small size of the tested sample (16 patients vs 16 controls, Supplementary Material-3).
This study is not without limitations. First, one should keep in mind that the diagnosis of depression is subjective, and subtypes of depression likely exist even though they have not been systematically distinguished. Likewise, the stratification of the patients by antidepressant classes performed here was not clean enough as the patients used different antidepressants. Second, this research is correlational and precludes causal relations between the neurobiology of MDD and aperiodic activity.

In conclusion, our findings suggest that flatter aperiodic slopes represent a new disease-relevant feature of sleep in MDD, which may reflect unstable, noisy neural activity due to a shift of the excitation-to-inhibition ratio in favor of excitation. In the future, these findings may lead to the development of a biomarker for personalized disease monitoring and therapy.

Acknowledgments

The first draft of this paper has been posted on medRxiv.

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Disclosure

The authors report no biomedical financial interests or potential conflicts of interest.

Contributors

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

Abbreviations

AUC – area under the curve

E/I – excitation-to-inhibition
HAM-D – Hamilton depression rating scale
MDD – major depressive disorder
NaSSA – noradrenergic and specific serotonergic antidepressants
NDRI – norepinephrine-dopamine reuptake inhibitor
REM – rapid eye movement
SNRI – serotonin-norepinephrine reuptake inhibitors
SSRI – selective serotonin reuptake inhibitors
TCA – tricyclic antidepressants
WASO – wakefulness after sleep onset

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Figure Legends
Figure 1. EEG power components. Total EEG spectral power (left), its aperiodic (right), and oscillatory (middle) components averaged over frontal electrodes are plotted in the log-log space as a function of frequency for non-REM (N2 + N3, first row) and REM (second row) sleep for each study group (different lines). Patients in both unmedicated (red lines) and medicated states (blue lines) show decreased oscillatory activity and steeper decay of the aperiodic component compared to controls (black lines). The total spectral power is comparable in all groups (coinciding lines of the left subgraphs).

Figure 2. Aperiodic slopes. Slopes of the broadband (0.2–48 Hz) aperiodic power component over each sleep stage and area for each study group. Unmedicated patients (red) show flatter (more positive values) slopes during N2 compared to controls (black). 7-day medicated patients (blue) show flatter slopes compared to their own unmedicated state (red) and controls (black) during all sleep stages – but not the wakefulness after sleep onset. MDD – 38 major depressive disorder patients, unmed. – unmedicated, med. – 7-day medicated MDD patients, HC – 38 healthy controls, F – frontal, C – central, P – parietal, O – occipital, T – temporal electrodes.

Figure 3. Effect of REM-suppressive medications. Slopes of the aperiodic power component in the 0.2-48Hz frequency band were averaged over each sleep stage over each area. Patients who take REM-suppressive antidepressants for 7-day (red, n=21) show flatter slopes (higher values) than patients who take REM non-suppressive antidepressants for 7-day (black, n=17) during all sleep stages – but not the wakefulness after sleep onset. F – frontal, C – central, P – parietal, O – occipital, T – temporal electrodes.
Table 1: Demographic, clinical, and sleep characteristics of the participants (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Unmedicated 7-day medicated</td>
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<tr>
<td>No. of participants</td>
<td>38</td>
<td>---</td>
</tr>
<tr>
<td>Age, years</td>
<td>31.3±10.2</td>
<td>---</td>
</tr>
<tr>
<td>Gender ratio, F/M</td>
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<td>---</td>
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<tr>
<td>HAM-D</td>
<td>19.9±3.8</td>
<td>15.2±4.8</td>
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<tr>
<td>No. of previous episodes</td>
<td>1.76±3.0</td>
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<tr>
<td>Non-REM-1, min (%)</td>
<td>52.38 (12.4%)</td>
<td>62.53 (15.0%)</td>
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<tr>
<td>Non-REM-2, min (%)</td>
<td>186.51 (44.1%)</td>
<td>201.03 (48.0%)</td>
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<tr>
<td>Non-REM-3, min (%)</td>
<td>76.64 (18.4%)</td>
<td>70.74 (17.2%)</td>
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<td>REM sleep, min (%)</td>
<td>68.93 (16.3%)</td>
<td>49.54 (11.8%)^{b,c}</td>
</tr>
<tr>
<td></td>
<td>WASO</td>
<td>Total non-REM time, min</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>WASO</td>
<td>37.83 (8.8%)</td>
<td>263.16 (68.2%)</td>
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<tr>
<td>Total non-REM</td>
<td>33.28 (8.0%)</td>
<td>271.76 (70.6%)</td>
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<tr>
<td>time, min</td>
<td></td>
<td>278.07 (69.7%)</td>
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</tbody>
</table>

Sleep stage percentages are given with respect to total sleep time. Non-REM sleep was defined as the combination of non-REM-2 and non-REM-3 without non-REM-1 sleep. SD – standard deviation, REM – rapid eye movement sleep, WASO – wakefulness after sleep onset, HAM-D – Hamilton Depression Rating Scale, a – significant difference between controls and unmedicated patients, b – significant difference between controls and medicated patients, c – significant difference between unmedicated and medicated states of the patients.
Table 2: Demographic and clinical characteristics of the subgroups of patients by medication class (mean ± SD)

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Sample size</th>
<th>Age</th>
<th>Gender</th>
<th>No. of previous episodes</th>
<th>HAM-D baseline</th>
<th>HAM-D 7-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI (citalopram, escitalopram, paroxetine, sertraline)</td>
<td>13</td>
<td>29.9±10.0</td>
<td>8 F</td>
<td>0.6±0.8</td>
<td>19.7±4.2</td>
<td>13.9±4.6</td>
</tr>
<tr>
<td>TCA (trimipramine, amitriptyline, amitriptylinoxide)</td>
<td>8</td>
<td>36.6±11.9</td>
<td>4 F</td>
<td>2.1±1.1</td>
<td>22.1±3.4</td>
<td>16.6±5.5</td>
</tr>
<tr>
<td>NDRI (bupropion)</td>
<td>6</td>
<td>30.7±10.5</td>
<td>3 F</td>
<td>0.7±0.5</td>
<td>18.5±3.5</td>
<td>17.8±3.2</td>
</tr>
<tr>
<td>SNRI (venlafaxine, duloxetine)</td>
<td>6</td>
<td>31.7±10.9</td>
<td>2 F</td>
<td>1.7±0.83</td>
<td>18.3±2.5</td>
<td>14.7±5.5</td>
</tr>
<tr>
<td>NaSSA (mirtazapine)</td>
<td>5</td>
<td>26.8±6.1</td>
<td>3 F</td>
<td>2.6±3.2</td>
<td>20.2±4.8</td>
<td>13.8±4.7</td>
</tr>
<tr>
<td>REM suppressive (SSRI, SNRI, amitriptylin, amitriptylinoxide)</td>
<td>21</td>
<td>31.1±10.3</td>
<td>11 F</td>
<td>1.1±1.0</td>
<td>19.2±3.6</td>
<td>14.1±4.5</td>
</tr>
<tr>
<td>REM non-suppressive</td>
<td>17</td>
<td>31.6±10.4</td>
<td>7 F</td>
<td>1.7±2.0</td>
<td>20.7±4.1</td>
<td>16.6±4.9</td>
</tr>
</tbody>
</table>

The NaSSA subgroup was not analyzed separately due to a small sample size.  
<table>
<thead>
<tr>
<th>Table 3: Aperiodic slopes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td><strong>Area/Stage</strong></td>
</tr>
<tr>
<td>Wake</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>REM</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
</tr>
<tr>
<td><strong>Area/Stage</strong></td>
</tr>
<tr>
<td>Wake</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>REM</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
</tr>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td><strong>F</strong></td>
</tr>
<tr>
<td>Wake</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>REM</td>
</tr>
</tbody>
</table>

**Bold** font indicates statistically significant p-values after the correction for multiple comparisons, effect sizes are interpreted as small (0.2–0.5), medium (0.5–0.8), and large (0.8–1.2). ^ ANCOVAs adjusted for the proportion of the corresponding sleep stage, MDD = major depressive disorder, HC = healthy controls, F = frontal, C = central, P = parietal, O = occipital, T = temporal electrodes, REM = rapid eye movement sleep, N = non–rapid eye movement sleep.
Table 4: Correlations between aperiodic slopes and sleep architecture (r)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unmedicated</td>
<td>Medicated</td>
</tr>
<tr>
<td>N1 slope – N1%</td>
<td>n.s.</td>
<td>0.347*</td>
</tr>
<tr>
<td>N1 slope – SWS onset</td>
<td>0.335*</td>
<td>0.351*</td>
</tr>
<tr>
<td>N2 slope – N1%</td>
<td>n.s.</td>
<td>0.479**</td>
</tr>
<tr>
<td>N2 slope – REM%</td>
<td>n.s.</td>
<td>-0.548**</td>
</tr>
<tr>
<td>N2 slope – REM onset</td>
<td>n.s.</td>
<td>0.391*</td>
</tr>
<tr>
<td>N2 slope – TST</td>
<td>n.s.</td>
<td>-0.328*</td>
</tr>
<tr>
<td>N3 slope – WASO</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>N3 slope – N1%</td>
<td>n.s.</td>
<td>0.455**</td>
</tr>
<tr>
<td>N3 slope – REM%</td>
<td>n.s.</td>
<td>-0.357*</td>
</tr>
</tbody>
</table>

Pearson correlations coefficients between aperiodic slopes measured during a particular sleep stage and features of sleep architecture are presented for each group separately. Only the r’s...
associated with the statistically significant p-values are presented, i.e., the rest of the possible combinations between aperiodic slopes and sleep architecture features were statistically non-significant, * – 0.05 > p > 0.01, ** – p < 0.01. Sleep stage percentages were calculated with respect to TST, TST – total sleep time, REM – rapid eye movement sleep, N – non-rapid eye movement sleep, WASO – wakefulness after sleep onset, r – Pearson correlation coefficient.