Magnetic seizure therapy and electroconvulsive therapy increase frontal aperiodic activity

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Data availability

All code used for all analyses and plots are publicly available on GitHub at https://github.com/voytekresearch/ect-mst. The data collected in this study is not available at this time.

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Author contributions

S.E.S., I.H., and B.V. conceived of the experiments and developed the analyses. I.H., R.Z., A.T.H., Z.J.D., and D.M.B., collected the data. S.E.S., E.L.K., Q.vE., and B.V. wrote analysis code and analyzed the data. S.E.S., E.L.K., Q.vE., I.H., and B.V. wrote the manuscript, and all authors edited the manuscript.

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Abstract

Major depressive disorder (MDD) is a leading cause of disability worldwide. One of the most efficacious treatments for treatment-resistant MDD is electroconvulsive therapy (ECT). Recently, magnetic seizure therapy (MST) was developed as an alternative to ECT due to its more favorable side effect profile. While these approaches have been very successful clinically, the neural mechanisms underlying their therapeutic effects are unknown. For example, clinical "slowing" of the electroencephalogram has been observed in both treatment modalities. A recent longitudinal study of a small cohort of ECT patients revealed that observed clinical slowing was better explained by increases in frontal aperiodic activity, an emerging EEG signal linked to neural inhibition. Here we investigate the role of aperiodic activity in a cohort of patients who received ECT and a cohort of patients who received MST treatment. We find that across treatments, frontal aperiodic activity better explains increases in delta band power associated with clinical slowing, compared to delta oscillations. Increased aperiodic activity is also linked to therapeutic efficacy, which is suggestive of a potential shared neural mechanism of action across ECT and MST: an increase in frontal inhibitory activity.

Introduction

Since its development in 1938, electroconvulsive therapy (ECT) has been used as a treatment for mood disorders including Major Depressive Disorder (MDD) and particularly, treatment-resistant depression (TRD)[1]. During a session of ECT, an electrical current is applied to the scalp of an anesthetized patient which induces a seizure as it passes through the brain. Despite the remission rates between 50-70%[2], it remains one of the least used treatments for depression. Fewer than 1% of patients with TRD receive ECT due to a combination of fear, stigma, and concerns about cognitive side effects, such as short-term amnesia[3]. The search for alternative, yet comparably effective, therapeutic stimulation techniques have led to the development of treatments like repetitive transcranial magnetic stimulation (rTMS) and more recently, magnetic seizure therapy (MST).

MST is a more focal treatment that was developed to mimic the therapeutic effects of ECT while minimizing the adverse side effects. Specifically, MST involves the application of a magnetic field to produce a seizure in the brain. The first person to receive MST was treated in 2000[4]. Compared to ECT, MST can produce remission rates as high as 50%[5] and patients receiving MST experience fewer cognitive side effects and recover more quickly after the procedure compared to patients receiving ECT[5–8](**Fig. 1**).

Many of the cognitive side effects of ECT are assumed to result from the induced seizure propagating widely through the cortex, particularly into the medial temporal lobes and hippocampus[7,9]. Although both ECT and MST induce a seizure, the characteristics of the induced seizure may differ between treatments[10] (**Fig. 1**). Specifically, when tested in nonhuman primates, analysis of intracranial electrodes implanted in the prefrontal cortex and hippocampus revealed that the seizure induced by MST had less

robust ictal expression than ECT and does not spread to the hippocampus[11] . Furthermore, indicators of pathological neuroplasticity in the hippocampus, including increased cell proliferation and fewer mossy fibers, were less pronounced in MST than ECT[11] . Anatomically realistic biophysical models of electrical current proliferation in ECT and MST support the findings in primates. In these simulations, compared to ECT, MST may avoid medial temporal and hippocampal regions, ultimately stimulating a much smaller portion of the brain which may minimize the negative side effects associated with bilateral ECT[12,13].

Beyond ictal expression, post-treatment electroencephalogram (EEG) recordings of both patients receiving ECT and MST are characterized by clinical "slowing," seen in increased spectral power in the delta (1-4 Hz) and theta (4-8 Hz) frequency ranges compared to baseline[14–16] . Sometimes, this increase in spectral power can be observed as apparent high amplitude delta and theta oscillations in the time domain[17,18] . However, this slowing has not been consistently linked to a mechanism of action or clinical efficacy for either treatment modality[19] .

However, previous investigations of band power changes have not considered the contributions of aperiodic activity to EEG signals. This is important because traditional analysis methods conflate periodic (oscillatory) activity with aperiodic activity[20,21] . This conflation occurs even in the absence of oscillations, which are not omnipresent, but rather appear infrequently in short bursts[22–24]. So even if there are no oscillations, a large aperiodic signal can appear very similar to slowing in the EEG, as we have recently demonstrated[25]. This effect occurs because the EEG signal is a mix of oscillations and aperiodic activity, where oscillations are defined by concentrated power with a specific, narrow frequency band. In contrast, aperiodic activity manifests as a broadband phenomenon, where power decreases exponentially as a function of frequency ($1/f^{\chi}$ scaling). This exponent is parameterized by χ (**Fig. 2A**), which naturally arises from the physiology of the EEG signal[26,27]. The EEG signal is largely composed of transmembrane postsynaptic currents that are characterized by their double-exponential form, the Fourier Transform of which naturally gives rise to $1/f^{\chi}$ scaling. The aperiodic exponent has been shown to at least partially capture the relative excitatory and inhibitory contributions to the local field potential[28,29], where an increase in the aperiodic exponent reflects a "steeping" rotation of the power spectrum. This corresponds to a shift toward greater inhibitory drive, and manifests as a large increase in low frequency power with a concomitant decrease in high frequency power (**Fig. 2B**).

Our recent investigation into longitudinal changes in aperiodic activity throughout a course of ECT revealed that many of the observations of increased frontal delta band power could be better explained by increases in frontal aperiodic activity[25]. Specifically, in that report, we found that the aperiodic exponent significantly increased longitudinally throughout the course of treatment. Furthermore, both aperiodic exponent at baseline and the magnitude of the change in exponent throughout treatment were related to treatment response, as measured by the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR). In comparison, there were no longitudinal effects in delta band power or oscillatory power. This was interpreted as evidence that longitudinal increases in frontal aperiodic activity may better explain clinical slowing observed in seizure-inducing treatments.

Here, we sought to replicate and extend that smaller (n = 9), longitudinal study in a larger sample of two independent datasets, one from a study of patients receiving ECT (n = 22)[30] and the other from a

registered clinical trial of patients receiving MST (n = 23)[31](Clinicaltrials.gov NCT01596608). We hypothesized that this recent finding would generalize to interventional findings of slowing in both ECT and MST. To test this hypothesis we compare measures of aperiodic activity, oscillations, and canonical band power. For each treatment modality, resting state EEG was collected at baseline and after completing a standard treatment, and analyses were restricted to frontal channels for replicability[25]. We find that in both ECT and MST treatment conditions, aperiodic exponent in frontal regions increases significantly and this change better explains observed delta (1-4 Hz) band power increases than power of a delta oscillation. We also find that theta (4-8 Hz) oscillations emerge following both ECT and MST. The magnitude of both of these effects was greater in ECT than in MST. Post-ECT EEG also contains more delta (1-4 Hz) oscillations and increases in alpha (8-12 Hz) oscillation power compared to baseline, a result not found in MST. These results highlight the relevance of changes in frontal aperiodic and oscillatory activity to stimulation treatments for depression and present promising opportunities for future research to better understand and differentiate the mechanisms of clinical efficacy and cognitive side effects.

Results

Clinical effects

For patients that received ECT treatment, the severity of depressive symptomatology as assessed by the clinician using the Hamilton Depression Rating Scale (HAMD-17) decreased significantly (pre = 24.26, post = 13.21, $t(18) = 5.94$, $d_z = 2.07$, $p = 1.3 \times 10^{-5}$) (**Fig. 1**, left, and **Table 1**). For patients that received MST treatment, HAMD-24 scores also decreased significantly (pre = 28.13, post = 21.40, $t(14) = 4.14$, $d_z = 0.93$, $p = 9.97 \times 10^{-4}$) (**Fig. 1**, right, and **Table 1**). Compared to MST, patients receiving ECT demonstrated greater clinical symptom improvements, as quantified by the relative change from baseline in HAMD-17 or HAMD-24 for ECT and MST, respectively (ECT = 44.02%, MST = 24.0%, $t(31.97) = 2.23$, $d_z = 0.75$, $p = 0.03$).

Treatment-related EEG effects: ECT

Compared to baseline, patients who receive a full course of ECT exhibit significant increases in aperiodic activity, as measured by the aperiodic exponent of power spectra in frontal electrodes, which become visibly steeper (pre = 0.89 μV^2Hz^{-1}, post = 1.56 μV^2Hz^{-1}, $t(21) = -8.12$, $d_z = 1.85$, $p = 6.15 \times 10^{-8}$) (**Fig. 3B**). We also observed concomitant increase in delta band power (pre = -11.91 μV^2Hz^{-1}, post = -10.97 μV^2Hz^{-1}, $t(21) = -8.03$, $d_z = 1.96$, $p = 7.69 \times 10^{-8}$) (**Fig. 3C**). However, very few patients had detectable delta oscillation peaks both at baseline and after treatment, which means that it is unlikely that clinical slowing reflects actual oscillatory processes (**Fig. 3D**). To determine whether the increases in delta band power were driven primarily by aperiodic activity or delta oscillation peaks, we computed delta abundance, defined as the fraction of frontal electrodes exhibiting a delta oscillation peak in their power

spectra, above the aperiodic signal. We found that delta abundance increases significantly post-ECT (pre = 0.03, post = 0.26, $t(21) = -3.16$, $d_z = 0.79$, $p = 4.75 \times 10^{-3}$) (**Fig. 3E**).

To further investigate how much of the observed changes in frontal delta band power, or slowing, was driven by aperiodic activity compared to delta oscillations, we performed a multiple linear regression to examine the contributions of delta oscillations and aperiodic activity to delta band power. This regression was significant overall ($R^2 = 0.59$, $F(2, 19) = 13.41$, $p = 2.33 \times 10^{-4}$), with the aperiodic exponent more significantly contributing to observations of increased delta band power ($\beta = 0.83$, $p = 0.003$) compared to delta abundance ($\beta = 0.48$, $p = 0.98$). That is, traditional band power definitions of delta, which do not seek to examine whether or not true oscillations are present, are better explained by non-oscillatory aperiodic activity in this sample. Furthermore, we performed similar multiple linear regressions to see whether frontal theta and alpha band power are better predicted by the change in aperiodic exponent, or the change in abundance of the respective frequency bands. Theta band power was also significantly related to a change in exponent, but not by the change in theta oscillation abundance. In contrast, alpha band power was not significantly related to the exponent, instead was related to a change in abundance and a change in oscillation power. This aligns with prior observations that alpha band power changes in human EEG are largely driven by actual alpha oscillations, whereas power in other bands is more related to aperiodic activity[32]. Full details of results are in the supplementary materials.

We also observed changes in frontal power in the theta and alpha ranges in patients who receive ECT. For patients whose EEG power spectra contained theta oscillation peaks before and after treatment, we observed significant increases in aperiodic-adjusted theta oscillation power (pre = 0.34 μV^2, post = 0.75 μV^2, $t(9) = -6.03$, $d_z = 2.03$, $p = 1.94 \times 10^{-4}$) (**Fig. 4A**). Similar to what we observed for delta, the fraction of electrodes that exhibited a theta oscillation peak also increased significantly with treatment (pre = 0.26, post = 0.63, $t(21) = -3.66$, $d_z = 1.00$, $p = 1.46 \times 10^{-3}$) (**Fig. 4B**). When we repeated this analysis in the alpha band, we found that alpha oscillation peaks decrease in power (pre = 1.21 μV^2, post = 0.83 μV^2, $t(21) = 3.81$, $d_z = 0.96$, $p = 1.03 \times 10^{-3}$) and abundance (pre = 1.0, post = 0.92, $t(21) = 2.41$, $d_z = 0.73$, $p = 0.025$) post-ECT compared to baseline (**Fig. 4 D-E**). This result is notable because alpha band power increases post-ECT when measured using the canonical bandpass approach (pre = -11.65 $\mu V^2 Hz^{-1}$, post = -11.42 $\mu V^2 Hz^{-1}$, $t(21) = -2.30$, $d_z = 0.47$, $p = 0.031$), highlighting the importance of spectral parameterization to disambiguate the contributions of periodic and aperiodic activity to band power, which separates band power into the periodic and aperiodic components.

Treatment-related EEG effects: MST

Similar to ECT, patients who were treated with MST (see Methods) exhibit a significant increase in the frontal aperiodic exponent compared to baseline (pre = 0.97 $\mu V^2 Hz^{-1}$, post = 1.16 $\mu V^2 Hz^{-1}$, $t(22) = -3.17$, $d_z = 0.80$, $p = 4.42 \times 10^{-3}$) (**Fig. 3G**). We also observe significant increases in delta band power (pre = -11.87 $\mu V^2 Hz^{-1}$, post = -11.64 $\mu V^2 Hz^{-1}$, $t(22) = -2.39$, $d_z = 0.58$, $p = 0.03$), but no significant change in delta abundance (pre = 0.01, post = 0.03, $t(22) = -2.05$, $d_z = 0.23$, $p = 0.18$) compared to baseline (**Fig. 3 H, J**). Furthermore, the multiple linear regression to relate delta band power to the aperiodic exponent and delta abundance was overall significant ($R^2 = 0.72$, $F(2, 20) = 26.21$, $p = 2.58 \times 10^{-6}$). Increases in aperiodic

activity (β = 1.27, p = 5.0 x 10^{-6}) better explain increases in delta band power than do changes in delta abundance (β = -1.66, p = 0.24), indicating that aperiodic activity is likely driving observed clinical slowing in MST as well. Similar to our ECT analysis, we performed multiple linear regressions to relate theta and alpha band power to the change in aperiodic exponent, or to the change in abundance of the respective frequency bands. We found that the aperiodic exponent was a significant predictor for both theta and alpha band power, while theta and alpha abundance did not significantly predict band power in each respective frequency band.

Although we do not observe significant changes in delta abundance, there were significant changes in theta oscillations. Specifically, both theta oscillation peak power (pre = 0.43 μV^2, post = 0.63 μV^2, t(12) = -4.71, d_z = 1.10, p = 6.39 x 10^{-4}) and abundance (pre = 0.31, post = 0.57, t(22) = -2.74, d_z = 0.65, p = 0.012) increase significantly post-MST compared to baseline (**Fig. 4 F-G**). This effect was similar to what we observe in ECT. However, unlike ECT, we observe no significant changes in alpha oscillation peak power (pre = 1.03 μV^2, post = 1.02 μV^2, t(22) = 0.21, d_z = 0.04, p = 0.83), nor in alpha abundance (pre = 1, post = 0.89, t(22) = 2.00, d_z = 0.59, p = 0.058), though the effect is marginal, post-MST (**Fig. 4 I-J**).

Lastly, we performed a t-test on the change in exponent between ECT and MST. The exponent change in ECT was significantly higher than for MST (ECT = 0.67 $\mu V^2 Hz^{-1}$, MST = 0.19 $\mu V^2 Hz^{-1}$, t(39.01) = 4.66, d_z = 1.40, p = 3.7 x 10^{-4}).

Clinical improvement and the spectral features in ECT and MST

To determine whether the observed changes in frontal aperiodic and oscillatory activity were related to overall treatment response independent of treatment modality, we computed a multiple linear regression to relate the relative magnitude of clinical improvement, as measured by the HAM-D, from the features that changed significantly after both ECT and MST, theta abundance and aperiodic exponent. We also included a term to account for a statistical interaction between change in aperiodic exponent and the number of treatments received. The overall regression was significant (R^2 = 0.24, F(3, 29) = 3.01, p = 0.046). We found that changes in aperiodic exponent (β = 0.67, p = 0.007) were predictive of treatment response (**Fig. 5**) but that theta abundance was not (β = -0.02, p = 0.91). In this model, patients who exhibit the greatest increases—or "steepening"—in aperiodic exponent after either ECT or MST treatment showed the greatest improvements in depression symptom severity, as measured by HAMD relative to baseline.

Furthermore, to determine whether any of the absolute, baseline EEG features could be identified as potential biophysical indicators of clinical treatment response, we performed a similar multiple linear regression using baseline measures of aperiodic exponent and theta abundance. Although trending, the model did not significantly predict treatment outcome from baseline measures (R^2 = 0.13, F(2, 31) = 2.34, p = 0.11). Within the model, baseline aperiodic exponent (β = -0.43, p = 0.040) significantly predicted clinical improvement (**Fig. 5**), but baseline theta abundance did not (β = 0.09, p = 0.55). In addition, we do find a significant correlation between baseline aperiodic exponent and treatment response across MST and ECT datasets (spearman's r = -0.36, p = 0.039), though this relationship should be interpreted with caution, as it is a simple correlation and has not been corrected for multiple comparisons. This

relationship indicates that patients who begin treatment with smaller aperiodic exponents—or "flatter" spectra—tend to be more responsive to treatment.

Discussion

The observation that frontal aperiodic activity increases after a course of ECT supports our recent finding from a smaller, longitudinal study[25]. Furthermore, similar observations after a course of MST identify the increase in aperiodic activity as a potentially informative physiological change shared by both of these seizure-based treatments for depression. For both ECT and MST, this increase in aperiodic activity is a more parsimonious explanation for observations of clinical slowing than delta band power or delta oscillations. Also, MST and ECT both induce increases in the power and abundance of theta oscillations. In addition to the changes in aperiodic activity and theta oscillations, ECT is associated with increases in the abundance of delta oscillations and decreases in the power of alpha oscillations. These effects are not observed in MST.

Aperiodic activity has been widely associated with behavioral and disease states, such as cognitive and perceptual task performance[33–36], development[37], aging[38], anesthesia[39], ADHD[40], and schizophrenia[41]. Furthermore, changes in aperiodic activity, like those observed in these two populations with MDD, have been associated with the physiological effects of deep brain stimulation as a treatment for MDD[42]. It is hypothesized that these aperiodic changes in the brain are related to the balance of excitation (E) and inhibition (I) based on simple computational models of the local field potential[28], complex microcircuit models[43] , and experimental manipulations of EI balance using optogenetics[29]. The changes in aperiodic activity seen in patients undergoing ECT and MST, specifically increases in aperiodic exponent visible as a "steepening" of the power spectrum, are associated with relative increases in inhibitory activity.

Therapeutic interventions that potentially increase inhibitory activity are particularly relevant in light of the cortical inhibition theory of depression. According to this theory, patients with MDD have insufficient inhibitory activity in various brain regions, particularly frontal cortices[44]. Post-mortem tissue analyses have revealed that these patients have pathologically reduced numbers of inhibitory, GABAergic neurons[45]. Specifically, these patients have reduced somatostatin-expressing (SST) interneurons in prefrontal cortices[46–48]. Simulated biophysical models of human microcircuits with reduced SST activity produce LFP signals with flatter power spectra and lower aperiodic exponents compared to control simulations of microcircuits with healthy SST populations[49]. Deficits in these inhibitory interneuron populations could cause pathological dysfunction in prefrontal EI balance. Because prefrontal cortices play an essential role in regulating EI balance throughout distributed networks in the brain[50], dysfunctional inhibition in prefrontal regions could lead to widespread disruptions, including in limbic structures[51] and the serotonergic and noradrenergic systems targeted by antidepressant medications[44]. Moreover, transcranial magnetic stimulation (TMS) concurrent with EEG also demonstrates decreased activation localized to frontal regions after successful neuromodulatory treatments for depression, and this attenuation is attributed to strengthening of inhibitory circuits[9,52].

Furthermore, we found that the degree to which a patient's frontal aperiodic activity increases post-treatment is related to the magnitude of therapeutic response, when controlling for the interaction of the aperiodic exponent with the number of treatments received. It should be noted that for the MST dataset, 61% of patients received exactly 24 treatments, the maximum under the study protocol, leading to an imbalanced number of treatments. However, the errors of the multiple linear regression model are normally distributed, thus mitigating the statistical effect of this imbalance. Previous analysis of the same ECT dataset has shown that the number of treatments correlates to more power in the slower frequencies. However, based on our re-analysis using spectral parameterization, we can interpret this slowing as an increase in the aperiodic activity[16]. Although interventional, this observation is in keeping with our recent longitudinal study and provides further evidence that aperiodic activity might be relevant to the therapeutic efficacy of ECT and MST. This clinical finding, combined with the computational and experimental evidence that identify aperiodic activity as an indicator of EI balance, suggest a promising mechanism of action for these stimulation treatments for depression. Specifically, we posit that ECT and MST ameliorate depressive symptoms by restoring healthy levels of inhibition in frontal regions, as measured by changes in aperiodic activity. Increasing levels of inhibition as measured through aperiodic activity align with observations of the anticonvulsant effects of ECT, with seizure induction threshold progressively increasing throughout a course of treatment[53].

Beyond identifying the physiological mechanism of ECT and MST, it is also vital to consider differences in the cognitive and physical side effects of these treatments. Previous studies suggest that the magnitude of therapeutic effects of ECT are unrelated to the severity of cognitive side effects[54], suggesting that these two phenomena are potentially dissociable. For instance, some theorists suggest that the therapeutic mechanisms of ECT are related to increases in delta power—an effect we argue is better explained by increases in aperiodic activity— and that cognitive side effects are driven mostly by theta power[55]. The observation that both ECT and MST produce increases in aperiodic activity that are related to clinical response supports the idea of a shared therapeutic mechanism. This effect is especially notable because the emergence of theta oscillations does not predict clinical efficacy. The differences we observed between ECT and MST in theta, as well as in delta and alpha oscillations, provide promising avenues for future investigation into the differential cognitive effects of these treatments. Theta oscillations, classically linked to memory[56], are of special interest here. The difference between ECT and MST in the post-treatment emergence of delta oscillations is also notable[7] and might be related to the amplitude and spatial distribution of the ictal activity during the induced seizure (**Fig. 1**). However, further investigation is needed to more precisely describe the contributions of oscillations and periodic activity to the therapeutic and cognitive effects of ECT and MST.

Unfortunately, the patients in the dataset included in this study were not thoroughly evaluated for cognitive and physical side effects so our analyses are limited to investigating therapeutic mechanisms. Furthermore, the data in this interventional study and the preceding longitudinal study can only speak to the short term effects of ECT and MST. More evidence is needed to determine how long changes in aperiodic and oscillatory activity persist post-treatment and if the longevity of these changes in EEG are linked to rates of MDD relapse. Furthermore, although we found similarities across ECT and MST, the increases in aperiodic exponent and theta oscillatory power were stronger in the patients who

underwent ECT. One potential explanation for this difference in magnitude could be that the ECT patients collected post-treatment EEG within 48 hours after the last session, while the MST patients waited longer on average to receive their post-treatment EEG, with an average of 3.81 days after the last session.

Future investigations can also explore the relationship of hemispheric differences and stimulation laterality to therapeutic efficacy and cognitive side effects. Because the vast majority of ECT and MST patients included in the study received bilateral stimulation, our analyses combined effects across frontal hemispheres. However, measures of hemispheric differences have been relevant to studies of depression, especially frontal alpha asymmetry, despite this measure being called into question by several recent meta analyses[57,58]. More evidence is needed to uncover the role of hemispheric differences in aperiodic and periodic activity in ECT and MST.

The current study shows that therapy-induced changes in frontal EEG aperiodic activity predicts clinical improvements in MDD patients undergoing ECT and MST treatment. Although not yet a viable clinical biomarker, the observed changes in aperiodic activity here provide further support for the cortical inhibition theory of depression[47]. Our results hint at potential physiological mechanisms of depression, and why ECT and MST are useful treatments, though much more physiological evidence is required. Furthermore, we show some important differences in the two treatments: Although MST may be less efficacious compared to ECT in terms of HAM-D improvement, MST still provides a significant therapeutic benefit, with potentially fewer adverse side effects.

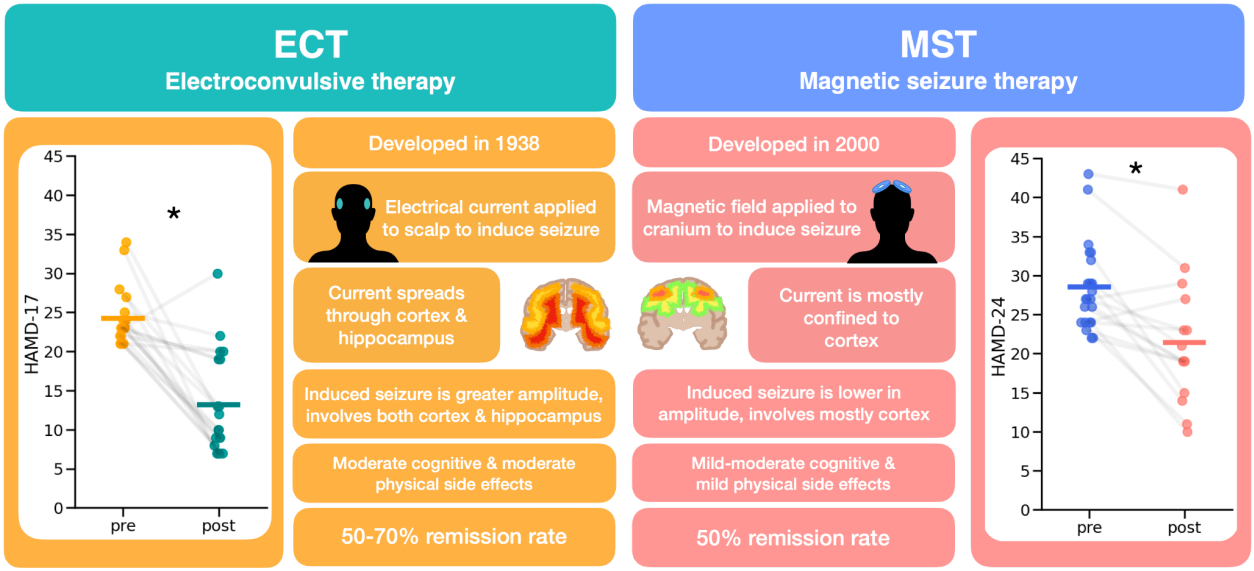


Fig. 1| ECT vs. MST. This figure highlights the most important similarities and differences between electroconvulsive therapy (ECT), and magnetic seizure therapy (MST). Both treatments are typically only used on patients with treatment-resistant depression and involve inducing a seizure, either with an electrical current or a magnetic field. The main difference is that ECT has a more global spread to subcortical structures and hippocampus, whereas MST affects more local cortical structures. However, both treatment types significantly reduce depression ratings, as measured by the HAMD-17 for ECT (pre = 24.26, post = 13.21, $t(18) = 5.94$, $d_z = 2.07$, $p = 1.3 \times 10^{-5}$) and the HAMD-24 for MST (pre = 28.13, post = 21.40, $t(14) = 4.14$, $d_z = 0.93$, $p = 9.97 \times 10^{-4}$).

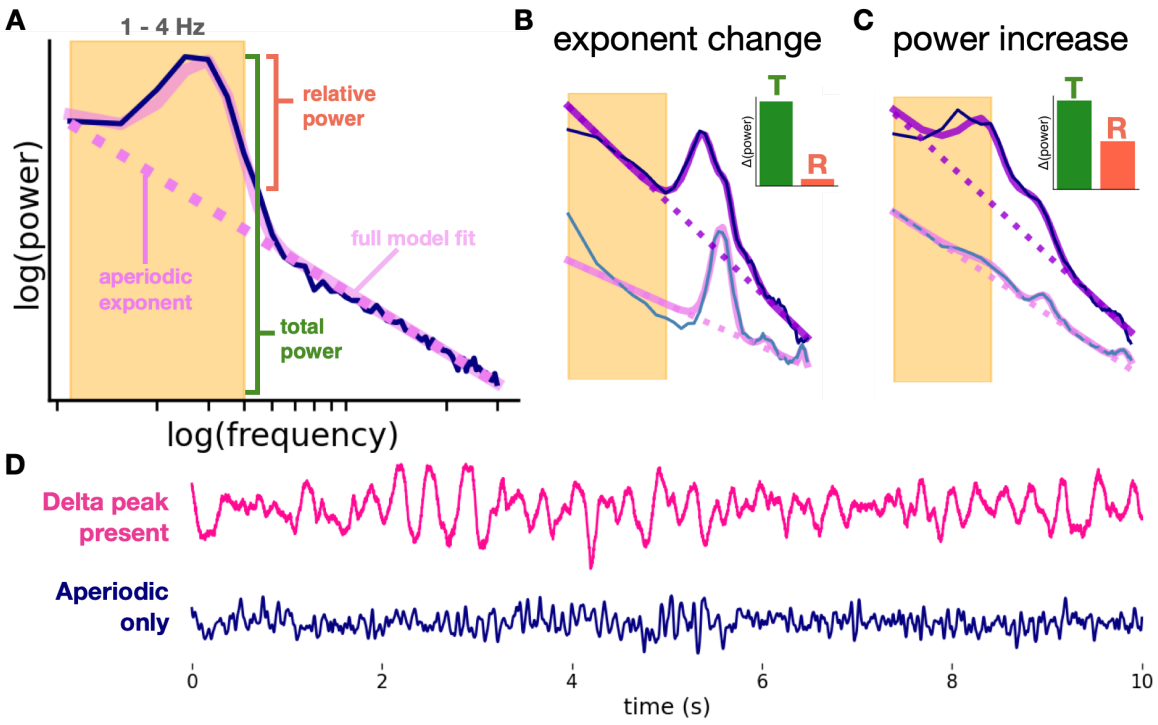


Fig. 2| Using spectral parameterization to disambiguate periodic and aperiodic contributions to delta band power. (A) Simulated power spectrum illustrating parameterized spectra. Unlike traditional band power measures that conflate periodic and aperiodic activity, spectral parameterization defines oscillatory power as relative power above the aperiodic component (pink dashed line). **(B)** Increases in the aperiodic exponent can cause apparent increases in total (T) band power, while power relative (R) to the aperiodic component remains unchanged. We see this here in the power spectrum averaged over frontal electrodes from one patient who exhibits an increase in exponent with no delta oscillation changes after treatment. **(C)** True increases in oscillatory power show increases in both total power and relative power. We see this here in the power spectrum averaged over frontal electrodes from one patient who exhibits an increase in delta oscillation power after treatment in addition to an increase in exponent. **(D)** Delta in the EEG trace vs. aperiodic activity. EEG with delta oscillations (where a delta peak is present in the spectra) is visibly different from EEG with only aperiodic activity in the delta band.

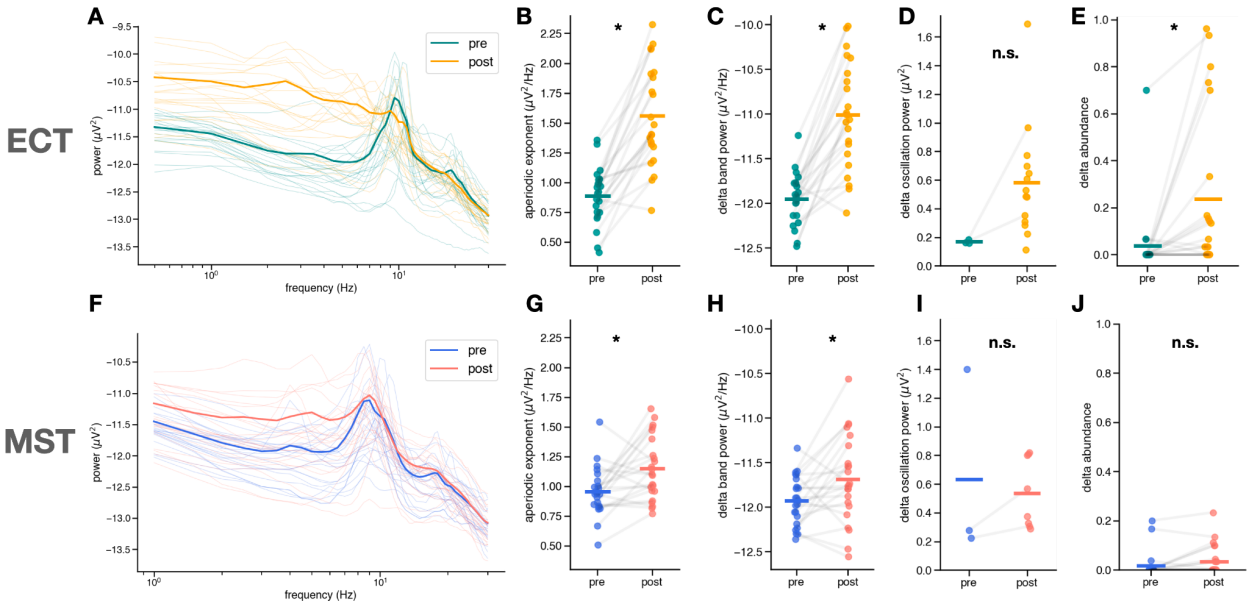
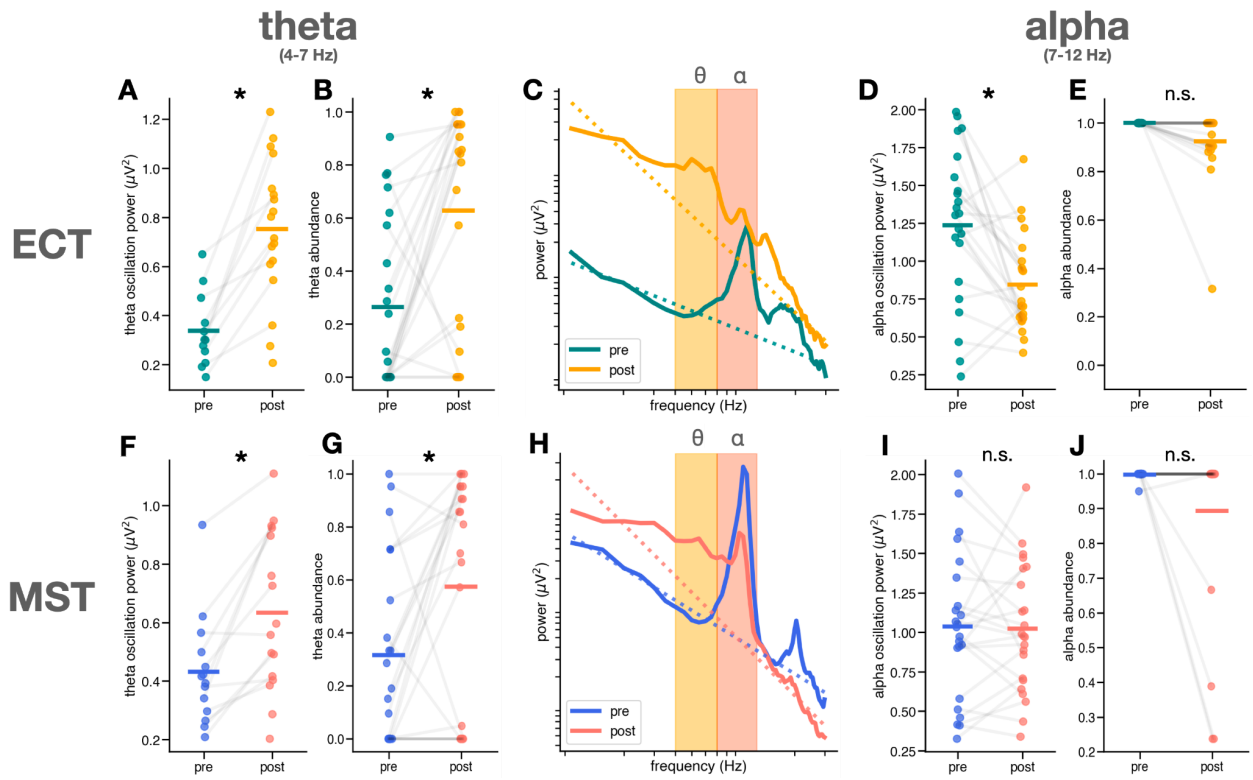


Fig. 3| EEG results - Aperiodic vs. delta band power slowing

Spectral differences in aperiodic exponent and delta oscillations in ECT (top) and MST (bottom). **(A)** Raw power spectra averaged across channels for each patient pre- and post-ECT. Bolded spectra represent average across patients. **(B)** Comparison of aperiodic exponent pre- and post-treatment (pre = 0.89 μV^2Hz^{-1}, post = 1.56 μV^2Hz^{-1}, t(21) = -8.12, d_z = 1.85, p = 6.15 x 10^{-8}), **(C)** total power in the delta band (pre = -11.91 μV^2Hz^{-1}, post = -10.97 μV^2Hz^{-1}, t(21) = -8.03, d_z = 1.96, p = 7.69 x 10^{-8}), **(D)** aperiodic-adjusted oscillatory power in the delta band (pre = 0.16 μV^2Hz^{-1}, post = 0.61 μV^2Hz^{-1}), and **(E)** abundance of delta oscillations (pre = 0.03, post = 0.26, t(21) = -3.16, d_z = 0.79, p = 4.75 x 10^{-3}). **(F)** Raw power spectra averaged across channels for each patient pre- and post-MST. Bolded spectra represent average across patients. **(G)** Comparison of aperiodic exponent pre- and post-treatment (pre = 0.97 μV^2Hz^{-1}, post = 1.16 μV^2Hz^{-1}, t(22) = -3.17, d_z = 0.80, p = 4.42 x 10^{-3}), **(H)** total power in the delta band (pre = -11.87 μV^2Hz^{-1}, post = -11.64 μV^2Hz^{-1}, t(22) = -2.39, d_z = 0.58, p = 0.03), **(I)** aperiodic-adjusted oscillatory power in the delta band (pre = 0.63 μV^2Hz^{-1}, post = 0.54 μV^2Hz^{-1}), and **(J)** abundance of delta oscillations (pre = 0.01, post = 0.03, t(22) = -2.05, d_z = 0.23, p = 0.18).



*

Fig. 4| EEG results - Emergence of theta and alpha oscillations

Changes in theta and alpha oscillations in ECT (top) and MST (bottom). **(A)** Comparison between theta oscillation power (4-7Hz) pre- and post-treatment (pre = 0.34 μV^2, post = 0.75 μV^2, t(9) = -6.03, d_z = 2.03, p = 1.94 x $10^{-4)}$, **(B)** theta abundance (pre = 0.26, post = 0.63, t(21) = -3.66, d_z = 1.00, p = 1.46 x 10^{-3}). **(C)** Power spectrum from frontal electrode F8 in a patient who received ECT. **(D)** Comparison between pre- and post-ECT alpha oscillation power (7-12 Hz) (pre = 1.21 μV^2, post = 0.83 μV^2, t(21) = 3.81, d_z = 0.96, p = 1.03 x 10^{-3}), and **(E)** alpha abundance (pre = 1.0, post = 0.92, t(21) = 2.41, d_z = 0.73, p = 0.025). **(F)** Comparison between theta oscillation power (4-7Hz) pre- and post-treatment (pre = 0.43 μV^2, post = 0.63 μV^2, t(12) = -4.71, d_z = 1.10, p = 6.39 x 10^{-4}), **(G)** theta abundance (pre = 0.31, post = 0.57, t(22) = -2.74, d_z = 0.65, p = 0.012). **(H)** Power spectrum from frontal electrode F8 in a patient who received MST. **(I)** Comparison between pre- and post-MST alpha oscillation power (7-12 Hz) (pre = 1.03 μV^2, post = 1.02 μV^2, t(22) = 0.21, d_z = 0.04, p = 0.83), and **(J)** alpha abundance (pre = 1, post = 0.89, t(22) = 2.00, d_z = 0.59, p = 0.058).

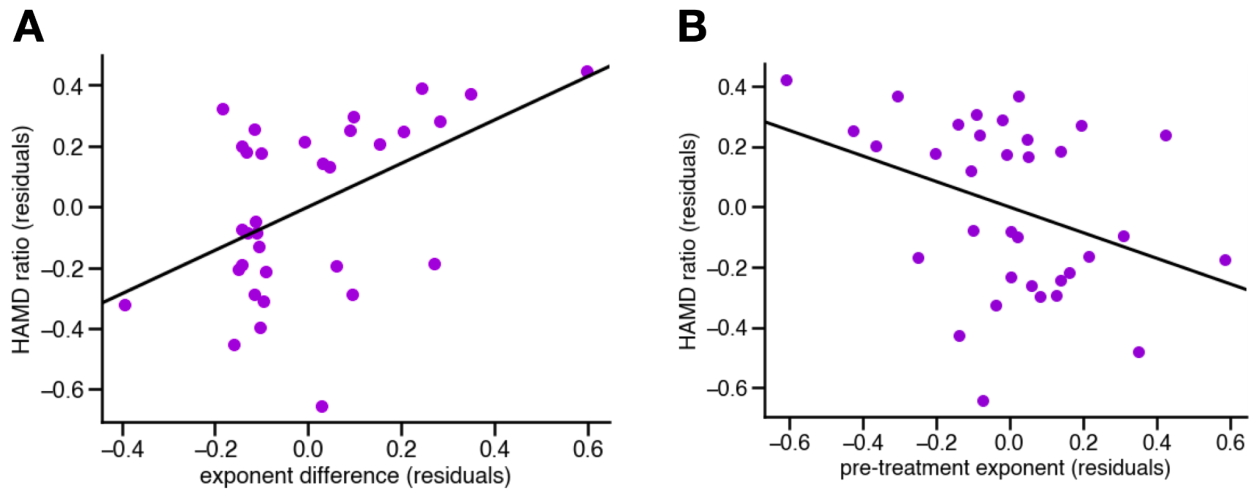


Fig. 5| Partial regression analysis - Exponent predicting treatment outcome

Change in aperiodic exponent and baseline aperiodic exponent significantly predict clinical outcome. **(A)** Partial regression showing a positive relationship between patients' change in aperiodic exponent, and clinical improvement, as measured by the ratio of pre- and post-treatment HAMD-17 and HAMD-24, for ECT and MST, respectively ($\beta = 0.67$, $p = 0.007$). Here, patients whose aperiodic exponents change the most (greatest spectral steepening) respond best to treatment. **(B)** Partial regression showing a negative relationship between patients' baseline aperiodic exponent, and clinical improvement, also measured by the ratio of pre- and post-treatment HAMD-17 and HAMD-24, for ECT and MST, respectively ($\beta = -0.43$, $p = 0.040$). Here, patients who begin treatment with lower aperiodic exponents (flatter spectra) at baseline respond best to treatment.

Table 1 | ECT and MST dataset details for patients included in this paper

ECT dataset details were from REF #16 and further correspondence. MST dataset details were from REF #9 and further correspondence.

ECT_n = 22; MST_n = 23	**ECT: Mean and SD**	**MST: Mean and SD**
Age	47.29 ± 16.75	46.13 ± 11.04
Gender (Male/Female)	9/14	16/15
HAM-D pre	24.25 ± 3.67 (HAMD-17)	28.52 ± 5.50 (HAMD-24)
HAM-D post	13.21 ± 6.56 (HAMD-17)	21.40 ± 8.14 (HAMD-24)
Number of treatments received	13.87 ± 5.32	18.80 ± 7.40
Responders	60.87%	45.16%
Medications		

Antidepressant	91%	61%
Antipsychotic	32%	26%
Anxiolytics	45%	17%
Stimulants	9%	13%
Sedative	27%	35%

Methods

Participants

Twenty-two patients who received a diagnosis of MDD as per the Diagnostic and Statistical Manual (DSM-IV) were included in this study for ECT. Twenty-three patients with the same diagnosis were included in this study for MST. Patients were considered as having treatment-resistant depression. Written informed consent was provided by all patients. Ethical approval was granted from the Centre for Addiction and Mental Health (CAMD) research ethics committee in accordance with the Declaration of Helsinki. A complete list of inclusions and exclusions criteria is provided in REF #30.

Electroconvulsive therapy

Patients received ECT 2-3 times per week. Square wave pulses were delivered using an open label protocol with a brief-pulse device (MECTA Corporation, Lake Eswego, OR). Patients started their treatment with either right unilateral ultra-brief pulse width ECT, or brief pulse width (1.0 msec) bi-temporal ECT based on the preference of the treating physician and the patient. Electrode placement was in accordance with American Psychiatric Association guidelines. Patients who received unilateral treatment were later switched to bi-temporal ECT if they showed an initial poor response to treatment. Anesthesia was induced by administering methohexital for sedation, and succinylcholine for muscle relaxation. Treatment completion was based on clinical factors, patient response, the patient's desire to discontinue treatment, or the most responsible physician's clinical judgment. More details about this process can be found in REF #30.

Magnetic seizure therapy

Patients received MST 2-3 times per week. A twin coil (Twin Coil-XS) was used with a MagPro MST stimulator (Magvenure, Denmark). The two coils were placed bilaterally over the prefrontal cortex, approximating F3 and F4 locations (international 10-20 system). Anesthesia was induced by administering methohexital sodium or methohexital plus remifentanil for sedation, and succinylcholine for muscle relaxation. Treatment completion was based on clinical factors, defined as a remission if the HAMD-24 score < 10 and greater than 60% reduction in depressive symptoms using HAMD-24 scale, or a

total of 24 treatments were administered. 61% of patients in this dataset received the maximum 24 treatments. More details can be found in REF #5,15.

Data acquisition

EEG data were collected within a week before patients started their treatment. For the ECT dataset, post treatment resting state EEG was collected within 48h after their last treatment. Whereas for the MST dataset, post treatment resting state EEG were collected on average 3.81 days (SD 3.86)[15] after their last treatment. A total of 10 minutes of resting state data with eyes closed were collected pre- and post-treatment. A 64-electrode cap (Neuroscan *Quik-Cap*) containing sintered Ag/AgCl electrodes connected to a SynAmpsˆ2 amplifier (Neuroscan, Compumedics, USA) was used for all recordings (online reference and ground electrodes located at the vertex, and just posterior to Fz, respectively). Impedances were maintained below 5kΩ throughout the recordings.

Clinical measures

Demographic and medication information were recorded at baseline during clinical interview (**Table 1**). For the ECT dataset, the primary clinical measure was the 17-item Hamilton Depression Rating Scale (HAMD-17), which was completed before the first treatment sessions, and within 48h after the last. For the MST dataset, the 24-item HAM-D was used. Because these datasets were collected independently, we assessed clinical improvement as a ratio of the change in depression severity relative to baseline as measured by the HAMD-17 or HAMD-24 for the ECT and MST datasets, respectively.

EEG pre-processing

EEG data was first downsampled to 1kHz. Then bad electrodes were identified and removed based on the presence of excess noise by inspecting the raw time series and the power spectra per electrode. After this, the data was re-referenced with the average method. Then, a FIR high-pass filter of 0.5 Hz was applied with a Hamming window. Fast ICA was used with 15 components to remove eye movements, eye blinks, and other non-neural artifacts. Lastly, the bad electrodes were interpolated.

EEG Spectral Parameterization

Power spectra were computed per patient for each electrode from the continuous EEG data using Welch's method, with a Hamming window of 2 seconds, and 1 second overlap between windows.

The spectral parameterization model was fit to each power spectrum between 1 and 30 Hz, without a knee, and oscillatory peaks were defined as peaks that surpassed a threshold of 0.05 μV^2 above the aperiodic component. A maximum of 12 peaks per fit with a minimum band width of 1 Hz and maximum of 8 Hz. On average, 3 peaks were found per power spectra, both pre- and post-treatment. Furthermore, the three frequency ranges of interest were delta (1 - 4 Hz), theta (4 - 7 Hz), and alpha (7 - 12 Hz). The peak with the highest power was selected within each frequency range. Model fits (R^2) below 0.8 were excluded from further analysis. One patient in the ECT dataset was completely removed from further analysis, due to excessive noise over the majority of the electrodes, which caused model fits below the threshold.

Canonical band power was calculated in addition to the metrics extracted using spectral parameterization methods for the purpose of comparing methodological approaches to quantifying spectral power. Band power was computed as the mean of spectral power in each frequency band (delta, theta, and alpha).

Electrodes of interest for further analysis were frontal (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FC5, FC3, FC1, FCZ, FC2, FC4, FC6). Further analysis was restricted to these electrodes because previous investigations found strong effects in frontal regions[25] and because both ECT and MST treatments target frontal cortical regions for stimulation. These electrodes were chosen to maintain consistency between the analyses in this study and the exploratory study in REF #25, and because prior research shows EEG effects of MDD treatment are strongest on frontal electrodes[59,60]. Prior to statistical analysis and visualization, features of interest were averaged across all included EEG electrodes for each patient.

Predicting band power based on aperiodic exponent and oscillation power

Band power is traditionally used to compute power within certain frequency ranges. Therefore, we wanted to include a regression to see whether it is the aperiodic exponent or actual oscillation power within a frequency range that predicts these band power measures. We did this for three frequency ranges of interest: delta, theta and alpha. For these regressions we used the change in exponent and the change in oscillation abundance. Furthermore for alpha power, because the abundance is so high, we also included oscillation power as a predictor. Thus, the formula for predicting delta band power is

$$\Delta_{delta\ band\ power} = \beta_0 + \beta_1\Delta_{exponent} + \beta_2\Delta_{delta\ abundance} + \varepsilon$$

The formula for predicting theta band power is

$$\Delta_{theta\ band\ power} = \beta_0 + \beta_1\Delta_{exponent} + \beta_2\Delta_{theta\ abundance} + \varepsilon$$

Last, the formula for predicting alpha band power is

$$\Delta_{alpha\ band\ power} = \beta_0 + \beta_1\Delta_{exponent} + \beta_2\Delta_{alpha\ abundance} + \beta_2\Delta_{alpha\ oscillation\ power} + \varepsilon$$

Predicting clinical outcome based on EEG spectral parameters

We used ordinary least squares regression to test whether and which changes in EEG spectral parameters predict clinical outcome. The dependent variable is the ratio of improvement on HAM-D scores. The predictors were the difference between pre- and post-treatment for the aperiodic exponent, theta abundance, and the interaction between exponent and the number of treatments:

$$\frac{HAMD_{pre} - HAMD_{post}}{HAMD_{pre}} = \beta_0 + \beta_1\Delta_{exponent} + \beta_2\Delta_{theta\ abundance} + \beta_3(\Delta_{exponent} \times N_{treatments\ received}) + \varepsilon$$

Furthermore, we also looked into EEG spectral parameters at baseline that could predict treatment outcome. For this we also looked at the ratio of improvement on HAMDscores, but without the interaction between exponent and number of treatments received:

$$\frac{HAMD_{pre} - HAMD_{post}}{HAMD_{pre}} = \beta_0 + \beta_1 exponent_{pre} + \beta_2 theta\ abundance_{pre} + \varepsilon$$

Statistical analysis

The dependent variables considered for analysis from the EEG signal are the aperiodic exponent, delta oscillation power, delta band power, theta oscillation power, theta band power, alpha oscillation power, and alpha band power. Furthermore, we calculated the fraction of frontal electrodes containing an oscillation per frequency band of interest (abundance).

All these parameters were calculated before the treatment started (pre), and after the treatment was completed (post). Normality was checked using the Shapiro-Wilk test. A paired t-test was performed on the pre- vs post-variables if the data was normally distributed, otherwise, a permutation test was used to determine statistical significance. The permutation null distribution was created by randomly changing the sign of the post- minus pre-features for 10,000 iterations. Additionally, t-tests were performed on the clinical outcome, and the change in exponent between ECT and MST, with a correction on the degrees of freedom for unequal sample sizes where appropriate.

Software

All EEG (pre-)processing, statistical analyses, and plotting was performed in Python (3.9.7), using MNE 0.24.1)[61], Spectral Parameterization (FOOOF; 1.0.0)[20], Pandas (1.3.2)[62], Pingouin (0.5.0)[63], Statsmodels (OSL) (0.13.1)[64], Matplotlib (3.4.2)[65], and Seaborn (0.11.2)[66].

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Supplementary material

ECT: The regression to predict theta band power was overall significant (R^2 = 0.8, F(2, 19) = 5.91, p = 0.010). An increase in aperiodic exponent significantly predicts theta band power measures (β = 0.66, p = 0.022), but not by theta abundance (β = 0.40, p = 0.081). For alpha band power, we were able to include the aperiodic adjusted alpha power, due to alpha's high abundance, which makes it a more reliable measurement. The overall regression was significant (R^2 = 0.50, F(3, 18) = 6.00, p = 5.11 x 10^{-3}). Alpha band power can be significantly predicted by both alpha aperiodic adjusted power (β = 0.52, p = 0.005), and by alpha abundance (β = -1.16, p = 0.043), but not by a change in exponent (β = 0.17, p = 0.42).

MST: The regression to predict theta band power was overall significant (R^2 = 0.70, F(2, 20) = 23.78, p = 5.16 x 1010^{-56}). A change in exponent significantly predicts theta band power (β = 1.39, p = 7.0 x 10^{-6}), but theta abundance did not (β = 0.13, p = 0.32). The regression for alpha band power was overall significant (R^2 = 0.46, F(3, 19) = 5.49, p = 6.88 x 10^{-3}). Both aperiodic exponent (β = 0.77, p = 0.003) and aperiodic adjusted alpha power (β = 0.59, p = 0.007) significantly predict alpha band power, but not alpha abundance (β = 0.22, p = 0.37).