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Modulation of neural oscillations in escitalopram treatment: a Canadian biomarker integration network in depression study

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Current pharmacological agents for depression have limited efficacy in achieving remission. Developing and validating new medications is challenging due to limited biological targets. This study aimed to link electrophysiological data and symptom improvement to better understand mechanisms underlying treatment response. Longitudinal changes in neural oscillations were assessed using resting-state electroencephalography (EEG) data from two Canadian Biomarker Integration Network in Depression studies, involving pharmacological and cognitive behavioral therapy (CBT) trials. Patients in the pharmacological trial received eight weeks of escitalopram, with treatment response defined as ≥ 50% decrease in Montgomery–Åsberg Depression Rating Scale (MADRS). Early (baseline to week 2) and late (baseline to week 8) changes in neural oscillation were investigated using relative power spectral measures. An association was found between an initial increase in theta and symptom improvement after 2 weeks. Additionally, late increases in delta and theta, along with a decrease in alpha, were linked to a reduction in MADRS after 8 weeks. These late changes were specifically observed in responders. To assess specificity, we extended our analysis to the independent CBT cohort. Responders exhibited an increase in delta and a decrease in alpha after 2 weeks. Furthermore, a late (baseline to week 16) decrease in alpha was associated with symptom improvement following CBT. Results suggest a common late decrease in alpha across both treatments, while modulatory effects in theta may be specific to escitalopram treatment. This study offers insights into electrophysiological markers indicating a favorable response to antidepressants, enhancing our comprehension of treatment response mechanisms in depression.

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INTRODUCTION

Major depressive disorder (MDD) is one of the most prevalent health conditions [1–3], affecting over 300 million people worldwide [4]. Medications are a first-line treatment for MDD. While many pharmacological agents, such as serotonin reuptake inhibitors (SSRIs), are available, they typically relieve depressive symptoms only after weeks or months [5]. Furthermore, first medication trials achieve remission in only about a third of patients, with subsequent trials still failing in approximately half [6]. Therefore, ongoing efforts focus on gaining a deeper understanding of the mechanisms underlying treatment response, ultimately aiming to reduce untreated depression and its enormous burden and cost to society and the individual.

Researchers have used electroencephalography (EEG) to gain insights into the dynamic functioning of the cortex. In addition to its ease of administration, wide availability, and cost-effectiveness, EEG allows for the study of fast cortical oscillations, which are a prominent feature of brain activity. These are believed to represent localized to long-range synchronization between neuronal populations and to play a critical role in both healthy behavior and disease states [7]. In the context of MDD, abnormalities in cortical oscillations have been observed in large-scale systems across different brain regions [8, 9]. By analyzing specific frequency oscillations, EEG provides valuable information for understanding how antidepressant interventions impact brain activity. For instance, alterations in alpha oscillations can indicate changes in the excitability/inhibition balance within cortical networks [10–13], influenced by serotonergic mechanisms [14–17]. Hence, cortical oscillations recorded in patients with MDD patients may provide useful information to better understand the impact of SSRI interventions on brain activity.

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To date, the study of cortical oscillations before treatment initiation has shown promise in predicting responses to various SSRIs [18–23]. Several authors have also questioned whether modulation of cortical oscillations can provide insight into the potential mechanisms of action of pharmacotherapies for depression. While late (≥4 weeks) modulation of cortical oscillations by pharmacological treatments has been explored [19, 24–26], more recent literature has focused on early (≤ 2 weeks) changes [18, 20, 27–31]. Collectively, a reduction in alpha oscillations is the most reported finding with different pharmacological treatments, including SSRIs. While less consistent, these previous studies also suggest pharmacological treatments may modulate slow oscillations, with an increase in theta power observed in response to SSRIs [20, 26].

Despite these advancements, challenges persist, including the variability in findings across studies and the limited understanding of how specific EEG changes translate into clinical improvement. For example, studies found responders to tricyclic imipramine and SSRI escitalopram treatments exhibited a greater increase in theta power after two weeks of treatment [18, 20], while a reduction in theta cordance after one week was associated with a response to serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, and SSRI fluoxetine [28–30]. Moreover, while older studies have explored late changes in EEG, recent research has tended to prioritize SSRIs predicting treatment outcomes over elucidating the neurophysiological mechanisms underlying symptom alleviation. Previous research has also often been constrained by small sample sizes (ranging from 18 to 70 participants) and focused on isolated aspects of neural oscillations or specific treatment phases. To gain a more comprehensive understanding of the link between neural oscillations and clinical improvement, larger-scale longitudinal studies that incorporate both early and late changes in the entire spectrum are warranted.

Hence, we set out to examine the early (2-week) and late (8-week) changes in the power of cortical oscillations in 125 patients with MDD undergoing eight weeks of treatment with the SSRI, escitalopram. These analyses constitute a prospective analysis of neurophysiological data collected from multiple centers across Canada as part of the first Canadian Biomarker Integration Network in Depression (CAN-BIND) study [32, 33]. Resting-state EEG data were collected at baseline, week 2, and week 8 for each participant. The severity of symptoms was evaluated at baseline, and every 2 weeks using the Montgomery–Åsberg Depression Rating Scale (MADRS). Successful response to escitalopram treatment was defined as a reduction of 50% or more in MADRS score from baseline to week 8. To assess the specificity of the findings, we compared the results from escitalopram-treated patients to an independent group of 37 patients with MDD who received sixteen weeks of cognitive behavioral therapy (CBT) for depression.

Building on prior research in SSRIs, we hypothesized that clinical improvements following escitalopram treatment would be associated with reductions in alpha activity and increases in theta activity at both early and late stages. We also hypothesized that changes in these frequency bands would be distinctive characteristics observed in responders to escitalopram. So far as we are aware, no study has investigated early or late changes in cortical oscillations through a course of CBT: hence we did not have a priori hypotheses regarding changes in EEG oscillations among CBT-treated patients. However, we speculated a possible reduction in alpha oscillations following CBT treatment, considering it might serve as a general marker of response to diverse antidepressant treatments [20, 26, 31, 34, 35].

METHODS

Participant sample for pharmacological treatment

Recruitment. Participants with MDD were recruited at 6 different sites in Canada: University of Calgary (UCA), University of British Columbia (UBC), McMaster University (MCU), Queen's University (QNS), Toronto General Hospital (TGH), and Centre for Addiction and Mental Health (CAMH). In addition, healthy controls were also recruited as part of the study. All participants gave written informed consent. The study protocol was approved by each institution's research ethics board and was in accordance with the Declaration of Helsinki. The study protocol was registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT01655706).

Eligibility. Participants with MDD had to be between 18 to 60 years old to be enrolled in the study, meet DSM-IV-TR criteria for a Major Depressive Episode of a least 3 months duration in Major Depressive Disorder (MDD) based on the Mini-International Neuropsychiatric Interview, be free of psychotropic medications for at least 5 half-lives before baseline visit, have a Montgomery–Åsberg Depression Rating Scale (MADRS) score equal or superior to 24, be fluent in English. Exclusion criteria can be found in the Supplementary Material. Healthy controls were also required to meet specific eligibility criteria, which are detailed in the Supplementary Material.

Pharmacological treatment. In the first eight weeks of this treatment trial, escitalopram was administered in an open-label manner, starting at 10 mg daily and increased to 20 mg daily at week two or later if clinically indicated. For patients unable to tolerate the 20 mg dose, a dose reduction to 10 mg was permitted at the treating psychiatrist's discretion. Participants were clinically assessed every two weeks throughout the study period (eight weeks). At the week eight visit, responder or non-responder status was determined (see [32, 33] for further details).

Participant sample for CBT treatment

Recruitment. Participants were recruited at CAMH and gave written informed consent. The study protocol was approved by the Centre for Addiction and Mental Health Research Ethics Board and was in accordance with the Declaration of Helsinki. The study protocol was registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02883257).

Eligibility. Participants had to be 18 years or older to be enrolled in the study. Inclusion criteria included were: (1) diagnosis of MDD or Persistent Depressive Disorder according to the Structured Clinical Interview for DSM-IV; (2) fluency in English; (3) capacity to give informed consent. Exclusion criteria can be found in the Supplementary Material.

CBT treatment. CBT was provided on an individual basis and delivered by a registered psychologist or graduate-level trainee under the direct supervision of a registered psychologist. Participants attended 2 sessions per week in the first 4 weeks and 1 session per week in the remaining 12 weeks, for a total of 20 sessions over 16 weeks (further details available in the Supplementary Material).

EEG data recording

EEG data were recorded during 5 min of resting-state, eyes-closed conditions at four sites for the pharmacological study (CAMH, TGH, QNS, UBC) and at CAMH for the CBT study. Recordings were conducted at baseline (within three days before treatment initiation), week two, and week eight for the pharmacological study, and at baseline, week two, and week sixteen for the CBT study. Four EEG devices with a minimum of 64 channels were used across sites (Supplementary Table S1). EEG data from healthy controls were used to assess the consistency of data quality across sites. Detailed results can be found in the Supplementary Material.

Inter-site data standardization and EEG data processing

As sites used different EEG devices, the datasets were standardized using the EEGLAB toolbox [36]. The EEG data were then cleaned using a customized, fully automatic pipeline which was adapted from the ERPEEG toolbox [37]. More details are given in the Supplementary Material.

EEG power spectral density

For each channel, Welch's periodograms with 2-sec overlapping windows and 0.5 Hz frequency resolution were used to estimate power spectral

Table 1. Demographics and clinical characteristics in the escitalopram cohort.

	Total ($n = 125$)		Responders ($n = 56$)		Non-responders ($n = 69$)		Test of difference	
Variable	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	**X^2**	***P***
Female	78	62.4	37	66.1	41	59.4	0.583	0.445
	Mean	SD	Mean	SD	Mean	SD	t	*P*
Age	36.4	13.0	36.1	13.2	36.7	12.8	−0.247	0.806
MADRS Week 0	30.0	5.8	29.4	5.8	30.5	5.8	−1.050	0.296
MADRS Week 2	23.3	8.5	20.2	8.4	25.8	7.8	−3.848	<0.001
MADRS Week 8	16.8	10.5	7.8	5.0	24.2	7.6		
−13.780							<0.001	%
Change in MADRS	44.2	32.7	73.5	16.0	20.5	21.5	15.290	<0.001

density (absolute power) from 0.5 to 50 Hz. The ratio of the absolute power of each frequency relative to the sum of absolute power across all frequencies was calculated to obtain relative power.

EEG source localization

Brainstorm software [38] was used to localize EEG sources for significant effects of interest. Additional details regarding preprocessing and applied statistic methods can be found in the Supplementary Material.

Statistical analysis

For each cohort, comparisons of demographic and clinical data between responder and non-responder groups were performed. Where appropriate, analyses were conducted using independent-samples t-test or Chi-squared test.

Escitalopram cohort. Mixed models with repeated measures were used to examine the effects of antidepressant response on relative power (0.5–50 Hz frequencies) for the main effect of Antidepressant Response (Responder, Non-Responder), Time (Baseline, Week 2, and Week 8), and the interaction effect of Antidepressant Response x Time; this was assessed separately across the 58 electrodes in the sensor space. For *post-hoc* comparisons, t-statistics were performed across all channels and frequency bands: delta band (0.5–4 Hz), theta band (4–8 Hz), alpha band (8–12 Hz), beta band (12–30 Hz), and gamma band (30–50 Hz). Within each frequency band, cluster-based non-parametric permutation tests were used to correct for multiple comparisons [39]. Significance was assigned to the probability of cluster sizes formed by pooling significant t-test results ($p < 0.025$, single-tailed) adjacent along all dimensions (channels x frequencies) of the data. The significance of each cluster was evaluated against the probability distribution of the largest clusters obtained over 2000 permutations. Identical parameters were used across all cluster-based permutation tests: threshold statistic of $p < 0.05$, a minimum of 2 neighboring significant sensors were considered for a selected sample to be included in a cluster, and 2000 permutations using the Monte Carlo approach, where cluster statistics were computed as the maximum sum of cluster t-values.

CBT Cohort. Similar to the above-described statistical analyses, mixed models with repeated measures were used to assess changes in relative power (0.5-50 Hz frequencies) throughout the course of CBT. The main effects of CBT Response (Responder, Non-Responder) and Time (Baseline, Week 2, and Week 16), and the interaction effect of CBT Response x Time were evaluated across frequencies (0.5-50 Hz) and 58 channels in the sensor space. *Post-hoc* comparisons were also performed using cluster-based non-parametric permutation testing.

Correlation analysis

Spearman's rank correlation coefficient was used to examine the association between the early and late change in relative power and the early and late percentage reduction (relative to baseline scores) in symptom severity with the escitalopram cohort. This association was studied for the five frequency bands separately and a cluster-based non-parametric permutation test was applied within each frequency band to correct for the multiple comparisons.

The same analyses were performed with the CBT cohort.

All analyses were performed using MATLAB (Version R2020b; MathWorks, Natick, MA, USA).

RESULTS

Demographic and clinical characteristics in escitalopram cohort

In total, one hundred and thirty-five participants were recruited at sites that collected EEG data. One hundred and twenty-five participants were included in the analysis (Table 1) with nine participants dropping out before completing week 8, and one participant lacking recorded EEG data. Fifty-six (45%) participants were classified responders, and sixty-nine (55%) were classified non-responders at week 8. No differences were observed between groups in sex ($p = 0.445$) or age ($p = 0.806$). Responders and non-responders did not differ in MADRS score at baseline ($p = 0.296$).

Demographic and clinical characteristics in CBT cohort

In total, forty-one participants were recruited. Thirty-seven completed the study and were included in the analysis (Supplementary Table S2). Twenty-two (59%) participants were responders, and fifteen (41%) were non-responders. No differences were observed between groups in sex ($p = 0.153$) or age ($p = 0.265$). Responders and non-responders did not differ in MADRS score at baseline ($p = 0.566$).

Changes in relative power over 8 weeks of escitalopram treatment

Using a mixed model with repeated measures analysis, significant ($p < 0.05$) main effects related to Antidepressant Response [mean F = 4.47 (3.92 to 7.36)] and Time [mean F = 3.69 (3.04 to 6.46)] were observed in a limited number of frequencies and channels in the sensor space. There was a significant interaction effect of Antidepressant Response x Time [mean F = 4.15 (3.04 to 7.84)] across several frequencies and channels in the sensor space. As such, *post-hoc* t-test analyses were performed for early (baseline to week 2) and late (baseline to week 8) changes within responder and non-responder groups. In what follows, the results of *post-hoc* analyses are presented in the sensor and source spaces. The average relative power EEG spectra per group at week 0, week 2, and week 8 can be found in Supplementary Fig S3.

Early changes. *Post-hoc* analysis did not reveal any significant early changes in responders or non-responders.

Late changes

Responders: *Post-hoc* analyses revealed late changes (from baseline to week 8) in responders, with a significant increase in the delta band (positive cluster, $p = 0.005$, Cohen $d = 0.361$, Fig. 1), a significant increase in the theta band (positive cluster, $p = 0.024$, Cohen $d = 0.295$, Fig. 1), and a significant decrease in the alpha

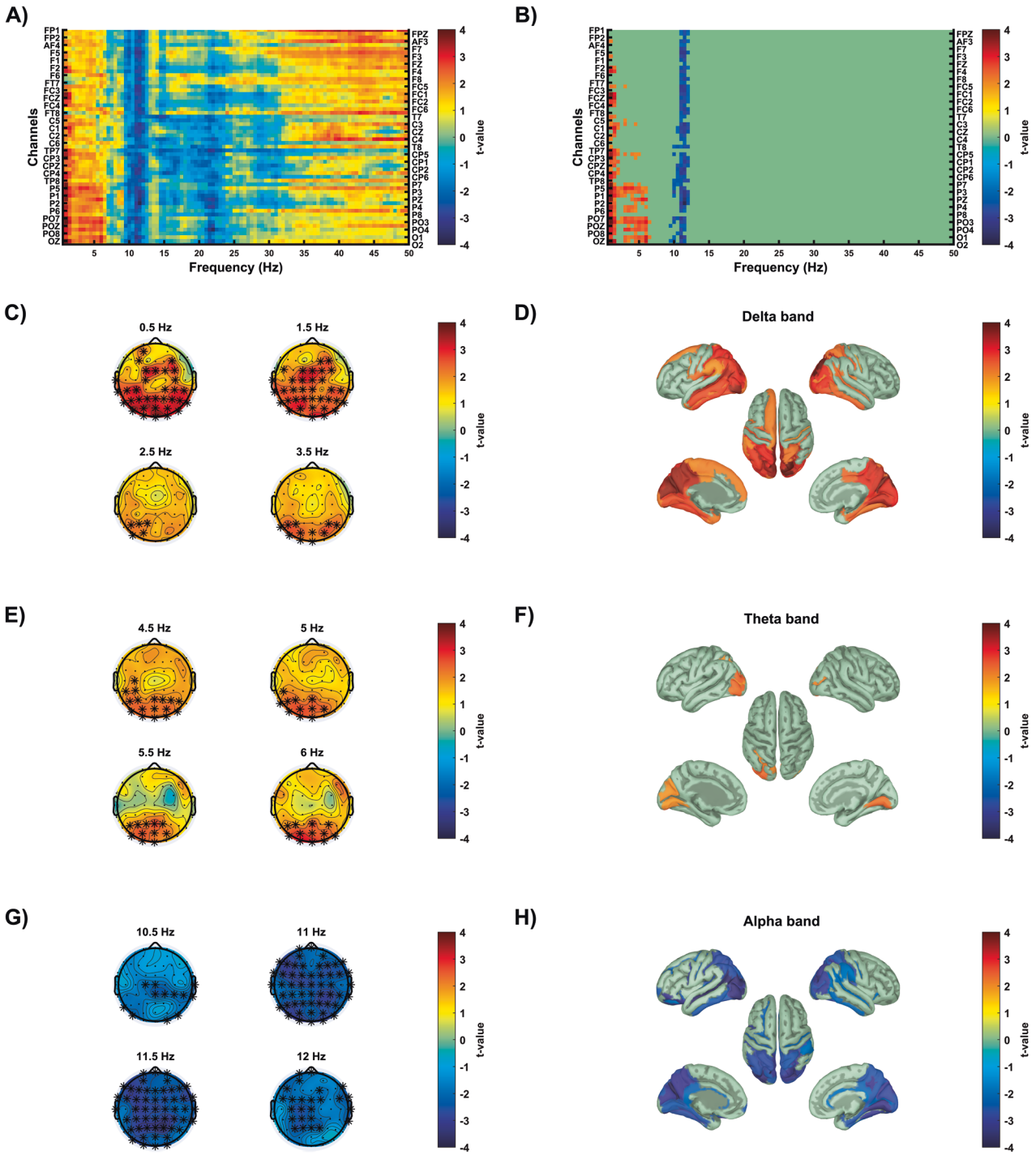

Fig. 1 Late changes (from baseline to week 8) in relative power in responders to escitalopram. Cold colors show lower relative power at week 8 compared to baseline. Warm colors show higher relative power at week 8 compared to baseline. **A**, **B** The x-axis shows frequencies from 0.5 to 50 Hz. The y-axis shows all electrodes from 1 to 58. Image A shows uncorrected t-value map, image B shows significant clusters ($p < 0.025$, single-tailed, cluster corrected for multiple comparisons). **C**, **E**, **G** Topographies illustrate t-values at different frequencies with stars indicating electrodes that belonged to the significant cluster. **D**, **F**, **H** Cortical maps depict source-localized regions ($p < 0.05$, uncorrected) in the frequency band in which the cluster was found at the sensor space level.

band (negative cluster, $p = 0.001$, Cohen $d = 0.339$, Fig. 1). In source space, changes in delta were localized to widespread regions in bilateral temporal, parietal, occipital, and cingulate cortices, as well as in the left frontal superior gyrus. Changes in theta were mostly identified in bilateral occipital poles and the left temporal lobe. Changes in alpha were also localized to widespread regions in bilateral temporal, parietal, occipital, and cingulate cortices, as well as in the left frontal superior gyrus, and left orbital frontal cortex.

Non-responders: Non-responders were found to exhibit a significant late increase in the gamma band (positive cluster,

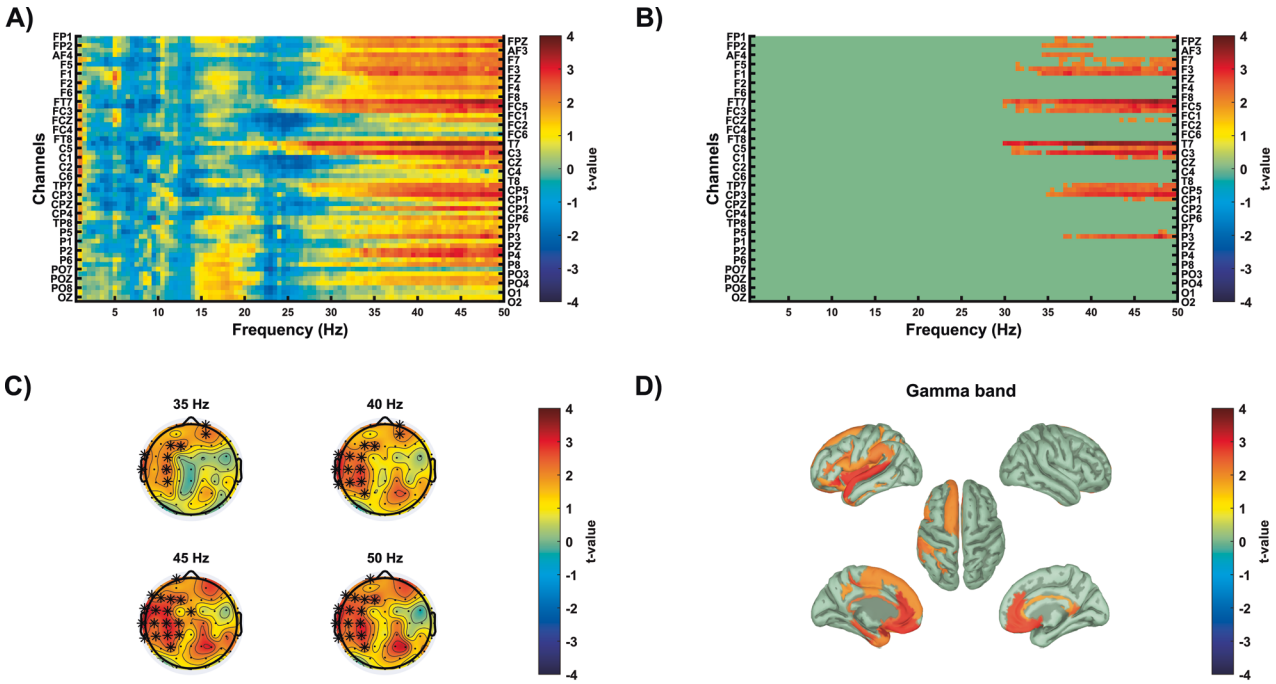

Fig. 2 Late changes (from baseline to week 8) in relative power in non-responders to escitalopram. Cold colors show lower relative power at week 8 compared to baseline. Warm colors show higher relative power at week 8 compared to baseline. **A**, **B** The x-axis shows frequencies from 0.5 to 50 Hz. The y-axis shows all electrodes from 1 to 58. Image A shows uncorrected t-value map, image B shows significant clusters ($p < 0.025$, single-tailed, cluster corrected for multiple comparisons). **C** Topographies illustrate t-values at different frequencies with stars indicating electrodes that belonged to the significant cluster. **D** Cortical maps depict source-localized regions ($p < 0.05$, uncorrected) in the frequency band in which the cluster was found at the sensor space level.

$p = 0.003$, Cohen d = 0.392, Fig. 2). This change was localized to widespread regions in the left hemisphere, as well as in the right cingulate cortex.

Changes in relative power over 16 weeks of CBT treatment

The mixed model with repeated measures analysis revealed significant main effects related to CBT Response and Time. Additionally, a significant ($p < 0.05$) interaction effect of CBT Response x Time was observed across several frequencies and channels in the sensor space. More details about the results are given in the Supplementary Material. *Post-hoc* t-tests and correlational analyses were performed for early changes (baseline to week 2) and late changes (baseline to week 16) within responder and non-responder groups. The average relative power EEG spectra per group at week 0, week 2, and week 16 can be found in Supplementary Fig S4.

Early changes in power

Responders: *Post-hoc* analysis revealed significant early changes in responders, with an increase in the delta band (positive cluster, $p = 0.019$, Cohen $d = 0.447$, Supplementary Fig S7) and a decrease in the alpha band (negative cluster, $p = 0.019$, Cohen $d = 0.291$, Supplementary Fig S7).

Non-responders: No early changes were found in non-responders.

Late changes in power

Responders: *Post-hoc* analysis revealed significant late changes in responders, with a decrease in low alpha (8–10 Hz) (negative cluster, $p < 0.001$, Cohen $d = 0.474$, Supplementary Fig. S8) and an increase in high alpha (10–12 Hz) (positive cluster, $p = 0.010$, Cohen $d = 0.474$, Supplementary Fig. S8).

Non-responders: No late changes were found in non-responders.

More details about the results can be found in the Supplementary Material.

Associations between changes in relative power and improvement in depressive symptoms with escitalopram treatment

After 2 weeks of treatment. The correlation analysis revealed significant associations between early changes in relative power and improvement in depressive symptoms after week 2. An early increase in theta (positive cluster, $p = 0.006$, mean rho = 0.217, Fig. 3), and an early decrease in gamma (negative cluster, $p = 0.020$, mean rho = −0.211 Fig. 3) were associated with percentage changes in MADRS score from baseline to week 2. The association in theta band was localized to widespread regions in bilateral frontal, central, temporal, parietal, and cingulate cortices (Fig. 3). The association in the gamma band was identified in several brain regions including the anterior cingulate cortex, bilateral frontal superior cortices, and right parietal and temporal cortices (Fig. 3). To investigate whether the observed associations were influenced by patients who exhibited a rapid response to treatment, a refined analysis was conducted by excluding individuals who demonstrated a positive response to escitalopram (50% or more reduction in MADRS) within the initial 4 weeks of treatment and were still responders at week 8 (Supplementary Material). Notably, the association between early theta increase and the percentage changes in MADRS score from baseline to week 2 persisted in this refined analysis (Supplementary Fig S6).

After 8 weeks of treatment. The correlation analysis revealed significant associations between late increases in the delta and theta bands and percentage changes in MADRS score from baseline to week 8 (positive cluster, $p = 0.018$, mean cluster

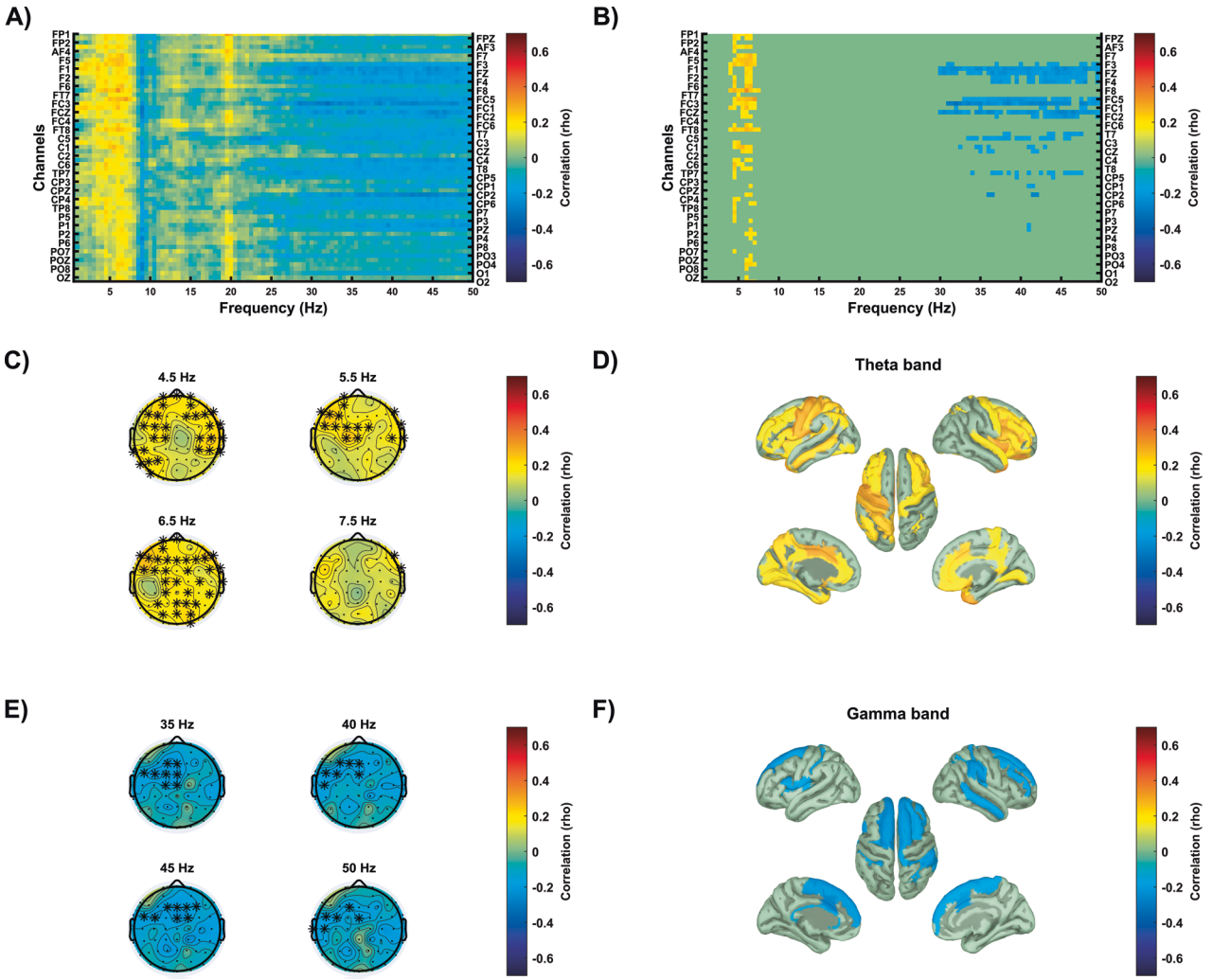

Fig. 3 Associations between early changes in relative power and improvement in depressive symptoms after 2 weeks of escitalopram. Cold colors show a negative correlation. Warm colors show a positive correlation. **A**, **B** The x-axis shows frequencies from 0.5 to 50 Hz. The y-axis shows all electrodes from 1 to 58. Image A shows uncorrected Spearman's correlation coefficients, image B shows significant clusters ($p < 0.025$, single-tailed, cluster corrected for multiple comparisons). **C**, **E** Topographies illustrate correlation coefficients at different frequencies with stars indicating electrodes that belonged to the significant cluster. **D**, **F** Cortical maps depict source-localized regions ($p < 0.05$, uncorrected) in the frequency band in which the cluster was found at the sensor space level.

rho = 0.225, and positive cluster, $p = 0.002$, mean cluster rho = 0.237, respectively Fig. 4). A significant association was also observed between a late decrease in alpha power and percentage changes in MADRS score from baseline to week 8 (negative cluster, $p = 0.008$, mean cluster rho = −0.244, Fig. 4). In the source space, the association was identified in several brain regions including, the left cuneus, left parietal inferior gyrus, left middle temporal gyrus, and left precentral and central sulci. The association in theta localized to widespread regions in bilateral temporal, parietal, occipital, and cingulate cortices. Finally, the association in alpha was mostly identified in the left postcentral gyrus, left middle occipital gyrus, and left temporal superior sulcus. (Fig. 4).

Associations between changes in relative power and improvement in depressive symptoms with CBT treatment

After 2 weeks of treatment. The correlation analysis did not reveal any association between early EEG power measures and percentage changes in MADRS scores from baseline to week 2 with CBT treatment.

After 16 weeks of treatment. The correlation analysis revealed significant associations between a late decrease in alpha power and improvement in depressive symptoms after week 16 (negative cluster, $p = 0.014$, mean rho = −0.459, Fig S9). More details about the results in the sensor and source spaces can be found in the Supplementary Material.

DISCUSSION

In this study, early and late changes in resting-state EEG neural activity throughout 8-week escitalopram treatment were investigated.

Late increases in slow oscillations (delta and theta) were associated with improvement in depressive symptoms after 8 weeks of escitalopram treatment. These late changes were specific to responders who exhibited significant increases in delta and theta activity after 8 weeks of treatment. This aligns with the findings of a previous study that showed increases in delta and theta to be associated with SSRI antidepressant response to 6 weeks of paroxetine treatment [26].

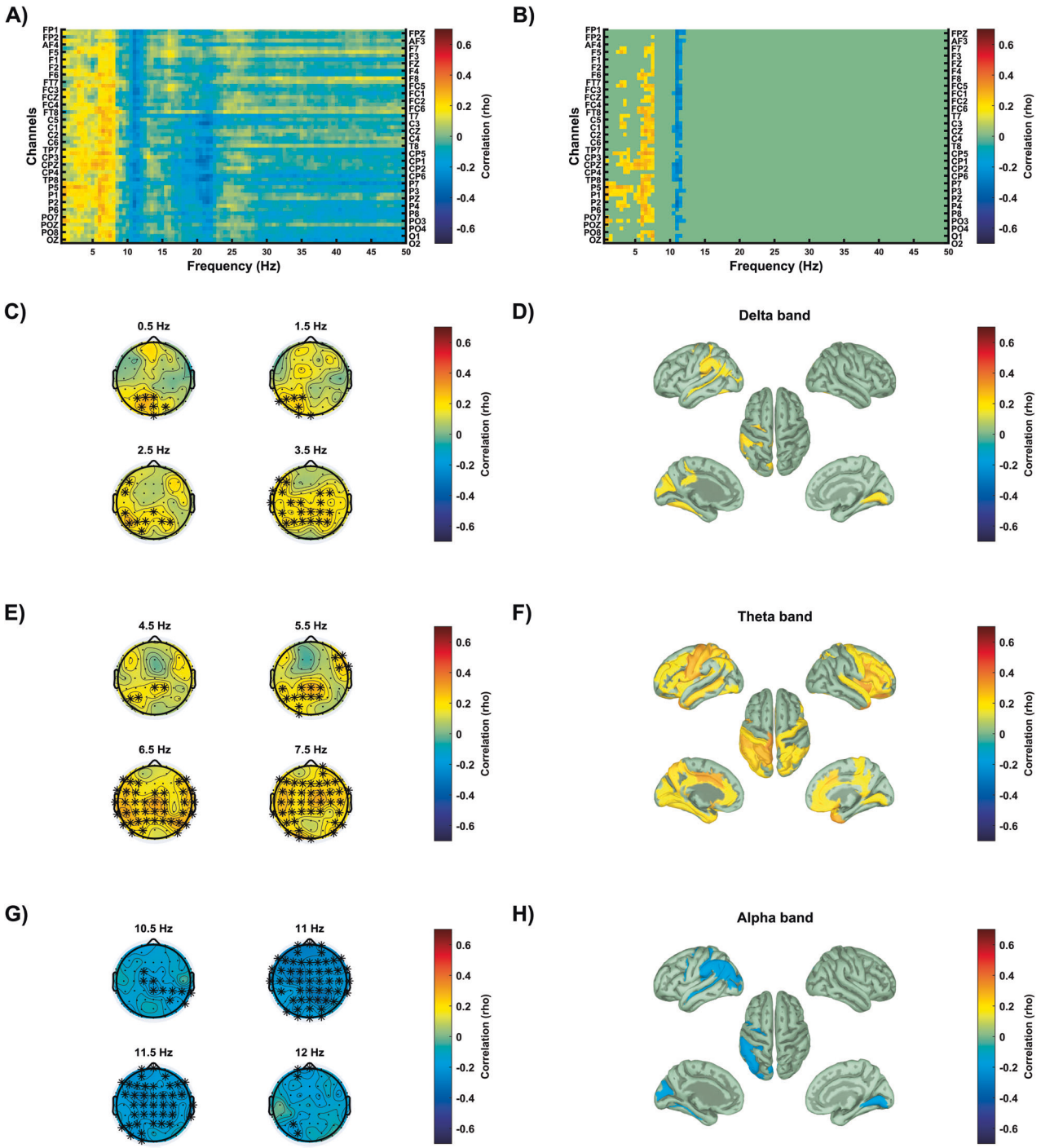

Fig. 4 Associations between late changes in relative power and improvement in depressive symptoms after 8 weeks of escitalopram. Cold colors show a negative correlation. Warm colors show a positive correlation. **A**, **B** The x-axis shows frequencies from 0.5 to 50 Hz. The y-axis shows all electrodes from 1 to 58. Image A shows uncorrected Spearman's correlation coefficients, image B shows significant clusters ($p < 0.025$, single-tailed) using cluster-based correction. **C**, **E**, **G** Topographies illustrate correlation coefficients at different frequencies with stars indicating electrodes that belonged to the significant cluster. **D**, **F**, **H** Cortical maps depict source-localized regions ($p < 0.05$) in the frequency band in which the cluster was found at the sensor space level.

Contrary to previous studies with imipramine and escitalopram [18, 20], early changes in theta were not observed in responders in our study. However, we identified an association between an early increase in theta activity and a greater reduction in MADRS score after 2 weeks of treatment. Importantly, this association persisted even after excluding patients with a rapid response to escitalopram treatment. This indicates that early theta activity changes remain linked to early reductions in MADRS, even in individuals who do not experience an immediate and pronounced alleviation. This underscores the potential relevance of theta activity modulation as a marker of early symptom improvement, extending beyond just the speed of response.

The primary literature linking theta oscillations to depressive symptoms involves a higher baseline theta power source

localized to the anterior cingulate cortex associated with improved treatment outcomes across different pharmacotherapies [31, 40, 41]. While responders to escitalopram did not exhibit higher baseline theta activity in our study, it is noteworthy that we observed an association between an increase in theta activity and improvement in symptoms, both early and late in the treatment. Collectively, these results contribute further evidence supporting substantial power modulation in theta activity throughout the course of SSRI treatment.

Furthermore, it is worth considering that diverse medications used in depression may exhibit varying degrees of efficacy in modulating slow oscillations. While our observations reveal late changes in slow oscillations, specifically in responders to SSRIs, no comparable late changes were noted in responders to CBT after 16 weeks of treatment. In CBT, as previously reported [42], only an early increase in delta oscillations was observed in responders. Contrastingly, treatments reserved for more difficult-to-treat cases, such as electroconvulsive therapy (ECT), have demonstrated distinct alterations. Notably, an association has been reported between the magnitude of ECT treatment response and an increase in delta oscillations in prefrontal regions [43]. Subsequent studies have highlighted a widespread increase in delta and theta activity in ECT, though these changes were not specific to responders [34, 44] These collective findings underscore the notion that different treatment modalities may engage distinct neural circuits or mechanisms, resulting in unique modulations of slow oscillatory activity.

In this study, late decreases in alpha power were shown to be associated with improvement in depressive symptoms after 8 weeks of treatment. Furthermore, these changes were specific to responders who exhibited a significant late decrease in alpha oscillations. This finding is largely in line with the literature on change in alpha power following other antidepressant modalities. In this study, both early and late reductions in alpha were also observed in responders to CBT. Additionally, late reduction in alpha was associated with improvement in depressive symptoms after 16 weeks of therapy. Regarding other antidepressant modalities, such as brain stimulation treatments, a previous study showed ECT to induce a widespread decrease in alpha power [34]. Meanwhile, another study on alpha-synchronized repetitive transcranial magnetic stimulation (rTMS) [35] reports a decrease in alpha power in the dorsolateral prefrontal cortex. These lines of evidence collectively suggest that successful antidepressant modalities may reduce the power of alpha oscillation. However, it is important to acknowledge the potential influence of symptom alleviation itself on this neural pattern, especially considering that prior studies lack placebo controls. Contrary to the hypothesis, early decreases in alpha activity were not observed in this study. Nevertheless, our study further complements these findings by demonstrating that the reduction of alpha oscillations, as observed in responders to escitalopram and CBT, may be associated with treatment efficacy. However, this may not happen as early as two weeks of escitalopram treatment.

Elevated cortical alpha oscillations are suggested to reflect cortical hypoactivity [45, 46]. Desynchronization in alpha oscillations (i.e., reduction in power of oscillations) is thought to reflect a release from cortical inhibition, which may indicate a shift toward processing external stimuli and cognitive engagement rather than internally self-focused emotional processing [10–13]. Medications used to treat depression may act via modulation of alpha oscillations that reflect a change in the relative excitation/inhibition balance within cortical networks, favoring cortical excitation. However, the precise mechanisms underlying how they influence alpha oscillations and contribute to normalizing cortical excitability are still not fully understood.

Studies in animals have demonstrated that serotonin may modulate neural oscillations [47–49], but its impact on cortical excitability is intricate, as it can induce both excitation and inhibition in interneurons and pyramidal cells [50]. Nevertheless, several serotonergic enhancers are suggested to decrease alpha power in the parieto-occipital regions during resting-state conditions [14–17]. Our findings with escitalopram support this observation. This modulation of posterior alpha oscillations could be particularly pertinent to perception, as alpha oscillations are known to play a crucial role in shaping visual processing [51, 52] and influencing cognitive functions [10, 53].

In this context, SSRIs may trigger cortical arousal through serotonin pathways, potentially leading to reductions in alpha that reflect increased engagement with external stimuli and cognitive processes. In contrast, CBT, a verbal and cognitive therapy, may achieve similar effects indirectly by redirecting cognitive focus. The observed alpha reduction in CBT responders may indicate a cognitive adaptation to better process external stimuli and tasks. While these speculations suggest different mechanisms for SSRI and CBT effects on alpha oscillations, more research is needed to fully understand these mechanisms and their impact on improving depressive symptoms.

This study also showed a significant association between an early decrease in gamma and a percentage reduction in MADRS score after 2 weeks. However, significant late increases were observed in gamma oscillations in non-responders. In contrast, patients who underwent CBT treatment did not exhibit any changes in gamma oscillations following the therapy. These results suggest a possible modulation of gamma by escitalopram, although it may not directly relate to the treatment's overall effectiveness in improving depressive symptoms. With respect to other antidepressants, suppression in gamma power was observed after mindfulness-based cognitive therapy for recurrent depression [54]. A study on unipolar depression demonstrated that a successful response to rTMS was associated with an increase in resting-state prefrontal gamma power [55]. Furthermore, subanesthetic ketamine doses were found to increase frontal gamma power both immediately and 2 h post-infusion in patients with treatment-resistant depression [56]. Additional studies are required to further explore the treatment-specificity of gamma oscillation modulations.

This study is notable for several reasons. Firstly, it is one of the largest longitudinal studies to date, involving over 100 participants receiving an SSRI treatment, which allows for more robust statistical analyses and enhances the generalizability of findings compared to previous studies with smaller sample sizes. Secondly, our study comprehensively examined both early (two-week) and late (eight-week) changes across all electrodes and frequency bands. This dual approach offers a more comprehensive understanding of how cortical oscillations evolve throughout antidepressant treatment, which has not been extensively explored in the literature. Finally, our study uniquely integrates findings from two distinct treatment modalities, SSRI pharmacotherapy, and CBT, allowing for a comparison of neurophysiological changes associated with these treatments. This comparative approach sheds light on whether observed EEG alterations are specific to pharmacological mechanisms or may also reflect broader mechanisms of treatment response in depression.

However, this study has limitations. Firstly, it was an open-label study and lacked a control group to further comment on the neurophysiology of placebo effects. Both CBT and escitalopram treatments were conducted in open-label designs, making it challenging to distinguish the specific effects of escitalopram from potential placebo responses. Randomized trials with appropriate control groups are needed to strengthen the reliability of our findings. Secondly, the CBT cohort in our study was relatively small with lower baseline MADRS scores compared to the escitalopram group. Additionally, the disparity in

treatment endpoints (week 8 for pharmacological treatment vs. week 16 for CBT) may introduce bias and limit generalizability to broader populations. Lastly, the study's specific exclusion criteria (see [33] for further details) may limit the generalizability of our findings to naturalistic treatment conditions. Therefore, any extrapolation of our findings to real-world clinical settings should be made with caution.

Looking ahead, future research could explore how changes in neural oscillations correlate with individual symptoms of depression, providing deeper insights into antidepressant mechanisms. Validating these associations would require larger sample sizes, and incorporating diverse demographic and clinical characteristics would enhance understanding across patient subgroups.

In conclusion, this longitudinal study supports the modulatory effects of SSRI treatments on resting-state cortical oscillations, highlighting potential mechanistic markers of escitalopram treatment response in individuals with MDD. Notably, these changes were identified through the utilization of EEG, an increasingly accessible technology in the field [57, 58]. Future studies could leverage EEG to expand on these findings, leading to the identification of robust biological targets. Techniques such as brain stimulation could then be employed to target and manipulate neural oscillations, such as theta and alpha, to alleviate specific depressive symptoms. While speculative, these hypotheses open new avenues for developing neurostimulation interventions tailored to individual neural profiles, potentially advancing more effective and personalized treatment strategies for MDD.

DATA AVAILABILITY

Researchers can access the CAN-BIND1 baseline eyes-closed resting-state EEG data used in this study through Brain-CODE at the following link: https://www.braincode.ca/content/controlled-data-releases#dr008. Access to data will be through a Brain-CODE Workspace.

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AUTHOR CONTRIBUTIONS

LCQ, PB, JAA, BNF, RWL, RM, DJM, CNS, SVP, GT, RU, SR, SHK, and FF designed the studies. BS, RC, YV, and SA contributed to the data analysis. BS, RC, PD, and FF wrote the manuscript. B.S. created all the figures. All authors (BS, RC, YV, LCQ, TAA, SRA, SA, PB, PD, JAF, BNF, SK, RWL, RM, DJM, CNS, CS. SVP, GT, RU, SR, SHK, and FF) reviewed and approved the final version of the manuscript.

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ETHICS DECLARATION

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

ADDITIONAL INFORMATION

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