UNIVERSITY OF CALIFORNIA

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# Using Quantitative Encephalography Measures to Predict Clinical Outcomes of Major Depressive Disorder in a Multi-Site Sertraline Trial

A thesis submitted in satisfaction of the requirements for the degree Master of Science in Bioengineering

by

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ABSTRACT OF THE THESIS

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Master of Science in Bioengineering
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Neuroimaging data has proven to be a useful biomarker for clinical outcomes in antidepressant treatment. Changes in quantitative electroencephalography (qEEG) measures such as delta-theta/alpha (DT/A) ratio and regional theta cordance have been associated with clinical improvement in patients with major depressive disorder (MDD). The relationship between changes in these measures after one week of treatment and remission or response was examined in a large cohort of subjects from the EMBARC study who received either placebo (N = 92) or sertraline (N = 86) treatment. A Week 1 decrease in central theta cordance from an 18-channel montage was associated with response in sertraline-treated subjects, but not placebo-treated subjects. However, neither DT/A ratio nor prefrontal theta cordance from a 30-channel montage

were predictive of remission or response in this dataset. These findings suggest that Week 1 changes in central theta cordance may serve as a biomarker for sertraline outcome in MDD patients.

The thesis of Bhavna Ramesh is approved.

Andrew Leuchter

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University of California, Los Angeles

2021

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## List of Acronyms

| | |
|---|---|
| MDD | Major depressive disorder |
| rTMS | Repetitive transcranial magnetic stimulation |
| CBT | Cognitive behavioral therapy |
| SSRI | Selective serotonin reuptake inhibitor |
| EEG | Electroencephalography |
| fMRI | Functional magnetic resonance imaging |
| PET | Positron emission tomography |
| FFT | Fast Fourier transform |
| ADHD | Attention-deficit hyperactive disorder |
| OCD | Obsessive compulsive disorder |
| rACC | Rostral anterior cingulate cortex |
| OFC | Orbitofrontal cortex |
| qEEG | Quantitative electroencephalography |
| DT/A | Delta-theta/alpha |
| rCBF | Regional cerebral blood flow |
| HAMD | Hamilton Rating Scale for Depression 17-item |
| IDS-SR | Inventory of Depressive Symptomology-Self-Report |
| CGI-I | Clinical Global Impression-Improvement Inventory |
| EMBARC | Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression |
| MRI | Magnetic resonance imaging |
| CU | Columbia University |

| | |
|---|---|
| MG | Massachusetts General Hospital |
| TX | University of Texas Southwestern Medical Center |
| UM | University of Michigan |
| FIBSER | Frequency, Intensity, and Burden of Side Effects Rating |
| FASTER | Fully Automated Statistical Thresholding for EEG artifact Rejection |
| ROC | Receiver operator curve |
| CC | Central theta cordance |
| DBS | Deep brain stimulation |

## Glossary

| | |
|---|---|
| **Absolute power** | Area under the power spectrum curve within a given frequency range |
| **Central theta cordance** | Theta cordance averaged across electrodes overlying the central region of the brain—specifically, Fz, C3, Pz, and C4 |
| **Cordance** | A qEEG measure of cerebral blood flow combining absolute and relative power |
| **Prefrontal theta cordance** | Theta cordance averaged across electrodes overlying the prefrontal region of the brain—specifically, FP1. FP2, and FPz |
| **Relative delta-theta/alpha ratio** | A power measure calculated by dividing the amount of relative delta-theta power by the amount of relative alpha power in an EEG signal |
| **Relative power** | The amount of absolute power in a given frequency band relative to the total absolute power across all four frequency bands |
| **Theta cordance** | Cordance calculated specifically in the theta frequency band (4-8 Hz) |

## Acknowledgments

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# Introduction

## 1.1 Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a highly prevalent mental illness characterized by changes in mood, sadness, an inability to experience pleasure, and other symptoms which greatly impact one's daily functioning [1]. More than 264 million people suffer from depression worldwide and the World Health Organization has labeled this disorder as a leading cause of disability in all populations [2][3]. While many treatments for MDD exist, including repetitive transcranial magnetic stimulation (rTMS) and cognitive behavioral therapy (CBT), to name a few, pharmacological treatments are often the first line of treatment for MDD, as they have been thoroughly studied and are typically more accessible than alternative treatment options [4]. One prominent class of antidepressants is selective serotonin reuptake inhibitors (SSRI). SSRIs are effective in treating chronic, moderate, and severe depression, and studies have shown that 40-60% with moderate to severe depression showed improvement in their symptoms after six to eight weeks of SSRI treatment [5].

While the efficacy of antidepressants has been demonstrated extensively, patients often must try several medications before discovering which one will work best for them. To overcome this obstacle, research has turned to biological markers such as cognitive deficits or structural and functional neuroimaging abnormalities to better understand how MDD presents itself among individuals. Identifying biomarkers that can help predict antidepressant response aids clinicians in providing a personalized course of treatment and subsequently reduces the time it takes for patients to receive effective treatment [6]. With most antidepressants, patients are at risk of experiencing some side effects, such as nausea, headaches, or insomnia, that may or may not improve over time [7]. Therefore, determining the best option for that patient early on in their

course of treatment is essential to alleviate the harmful symptoms of depression and reduce the chances of a patient experiencing any adverse side effects more than once.

### 1.2 Electroencephalography (EEG) and MDD

One widely used neuroimaging tool for identifying biomarkers of depression is electroencephalography (EEG). EEG measures the electrical activity of neurons from the scalp by characterizing neural oscillations, which represent the balance of excitation and inhibition produced through the synchronous firing of neuronal populations and are assumed to be sinusoidal in shape [8][9]. Although it has lower spatial resolution relative to other neuroimaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), EEG has a very high temporal resolution that provides information on a neuronal scale and is noninvasive, quick, cost-effective, and generally better tolerated by clinical patients [10][11]. EEG signals are typically recorded using an elastic cap embedded with several electrodes connected to one another that is placed on the head, and the number of electrodes on an EEG headset can vary significantly [12][13].

EEG signals, which are typically recorded in units of voltage and contain a frequency component, have corresponding power spectrums, which can be analyzed by applying a linear magnitude fast Fourier transform (FFT) to the original EEG waveform, which will output spectral peaks corresponding to the frequencies of oscillations that are present in the data [14]. The EEG signal is often characterized by the following spectral bands for ease of analysis: delta (1.3-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), beta (12.5-30 Hz), and gamma (30-40 Hz) [15]. It is important to note that the upper and lower limits of the frequency bands may vary slightly across studies or clinical populations. Delta and theta frequencies are commonly associated with sleep or drowsiness, alpha frequencies are present during an awake and alert state, and beta

frequencies are present during active thinking [16]. Studies with EEG typically conduct power analyses in each of the frequency bands to better understand the complex EEG waveform, with power calculated as the squared amplitude of the oscillations, which represents the strength of a frequency found in the signal [17][18]. Absolute and relative power are often calculated in each of the frequency bands, where absolute power is the area under the power spectrum curve within a given frequency range, and relative power represents the amount of absolute power in a given frequency band relative to the total absolute power across all four frequency bands [19].

Understanding the extent to which a specific frequency is present in a signal through patterns or differences in power during tasks or certain brain events (such as seizures) provides insight into the activation of or connectivity between specific brain regions [20]. EEG spectral data have also been associated with certain emotional states and are therefore extensively analyzed as a biomarker for various psychiatric disorders such as depression, attention deficit-hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and more [15][21][22]. Various studies have investigated the relationship between EEG measures and depression to determine what biomarkers may predict the onset or progression of MDD, and these studies operate on the basis that serotonin has been shown to play a significant role in rhythmic oscillations of the brain in the range of 2.5-12 Hz, which encompasses delta, theta, and alpha activity [23][24]. For example, several studies found a relationship between SSRI treatment and changes in prefrontal oscillations in the delta, theta, or alpha frequency bands [25][26][27].

### 1.3 Previous Work Studying EEG Measures as Biomarkers of MDD

There is significant evidence that higher posterior baseline alpha power characterizes antidepressant responders but not non-responders, suggesting that analyzing changes in alpha power in certain regions of the brain could be relevant to identifying EEG biomarkers of MDD

[28][29][30][31]. Furthermore, it has been hypothesized that frontal alpha power asymmetry is linked to deficits in reward processing, which is a key characteristic of depression onset [32]. Additionally, because certain emotional states can influence attention, studying the lower end of frequencies in the alpha band, which was found to reflect certain features of attention, specifically vigilance and expectations, may be important in understanding MDD [33][34].

With respect to the theta frequency band, one study found greater theta current density in the rostral anterior cingulate cortex (rACC) and orbitofrontal cortex (OFC) in patients who responded to antidepressants [35]. These findings were further supported by a meta-analysis that found 19 studies highlighting the relationship between increased pre-treatment rACC activity and antidepressant response [36]. Another study found that greater pre-treatment relative delta power in the right hemisphere was associated with treatment responders while the opposite was associated with non-responders [37]. Together, these studies reflect the well-established link between SSRIs and EEG measures, thus setting the precedent for further research into the use of certain EEG biomarkers for predicting the course of treatment of MDD with antidepressants.

One prominent study analyzed if quantitative encephalography (qEEG) data, which is obtained through the processing of digital EEG signals using complex computer algorithms, in patients treated with the SSRI escitalopram were correlated with any changes in or remission of symptoms of MDD relative to patients treated with only placebo [38][39]. The researchers explored changes in relative prefrontal delta-theta and alpha power as well as the delta-theta/alpha ratio for the different treatment groups. As mentioned before, the effects of serotonin have been pronounced in these frequency bands; therefore, shifts in the balance between the slower (delta and theta) and faster (alpha) wave bands could be associated with improved physiological response to treatment. Researchers found that average prefrontal delta-theta power

increased significantly after one week of active treatment while alpha power decreased. Neither of these measures were found to have changed significantly with placebo treatment. More specifically, the study found that increases in the delta-theta/alpha (DT/A) ratio early on in treatment were associated with non-remission after seven weeks of treatment with medication [39].

### 1.4 Cordance and MDD

Although power has proven to be a useful measurement of brain activity, its relationship to other physiological correlates of electrical activity such as cerebral blood flow (perfusion) or energy metabolism has not been thoroughly explored. In order to better understand and characterize this relationship, another qEEG measure of electrical activity called cordance was developed [40]. Specifically, cordance combines absolute and relative power measures using a three-step algorithm detailed by Leuchter, et al 1994. First, absolute power for each bipolar pair (denoted by lines connecting electrodes as in Figs. 1 and 2) was calculated. Then, the absolute power for each electrode pair that included a single electrode was averaged to obtain a single re-attributed power value for that electrode. Secondly, relative EEG power was calculated based on the reattributed absolute power values. The absolute and relative power values were then z-transformed for each electrode, resulting in normalized absolute ($A_{norm}$) and relative power ($R_{norm}$) values. Finally, z-score values were summed ($A_{norm} + R_{norm}$) to obtain a cordance value, Z, at each electrode [26][40][41].

This measure is sensitive to cortical deafferentation, or the interruption of nerve afferents in the cerebral cortex, and provides information on levels of brain activity [40][42]. The algorithm outputs a numerical value that is either negative (associated with a “discordant” state that reflects low perfusion or metabolism) or positive (associated with a “concordant” state that

reflects high perfusion or metabolism) at each of the recording electrodes. Cordance is studied within each of the EEG frequency bands; for example, theta cordance reflects the relative and absolute power derived from the theta frequency band (4-8 Hz). Studies using PET neuroimaging techniques have found abnormal regional cerebral blood flow (rCBF) and metabolic changes in depressed patients, particularly in prefrontal brain regions like the anterior cingulate cortex, the dorsolateral prefrontal cortex, and frontal gyri, which are known to be involved in mood regulation and the progression of depression [43][44][45][46][47][48]. Together, such findings suggest that studying cerebral perfusion and metabolism through a measure such as cordance can be important in predicting treatment response.

A study of cordance in patients with major depressive disorder found that a reduction in prefrontal theta cordance was predictive of bupropion treatment response [49]. In contrast, a separate study showed that non-responders to escitalopram treatment displayed an early increase in prefrontal theta cordance [37]. A more recent study investigated changes in prefrontal and midline right frontal theta cordance at the start of treatment and changes in depressive symptoms and found that the combination of the three was most predictive of response to escitalopram, bupropion, or a combination of the two [50]. Of the studies analyzing cordance data and MDD outcome, one analyzed the role of absolute theta power, relative theta power, and theta cordance across specific regions as indicators of clinical response to treatment with medications fluoxetine or venlafaxine or a placebo drug. qEEG data were collected prior to treatment, 48 hours after treatment, and one-week post-treatment. The clinical outcome of interest was a final Hamilton Rating Scale for Depression 17-item (HAMD) score less than or equal to 10, and theta cordance was measured using a 35-channel montage. Subjects were grouped according to the following groups: placebo responders, placebo non-responders, medication responders, and medication

non-responders. Results found that although changes in theta power did not show a significant association with clinical outcome in any of the subject groups, changes in prefrontal theta cordance were associated with the medication responder group. These findings suggest that prefrontal theta cordance may play a role in response to antidepressant treatment [26].

A more recent study analyzed the effects of rTMS instead of pharmacological treatment on clinical outcome for major depressive disorder using solely the qEEG measure of theta cordance [41]. qEEG data from a 21-electrode montage were collected prior to rTMS treatment and one-week post-treatment and clinical outcomes were obtained from the Inventory of Depressive Symptomology-Self-Report (IDS-SR) score and the Clinical Global Impression-Improvement Inventory (CGI-I). Cordance was measured across electrode groupings that corresponded to the following spatial regions of the brain: prefrontal, midline-and-right-frontal, midline-and-left-frontal, central, orbital, midline-and-right-orbital, and midline-and-left-orbital. Results found that a decrease in theta cordance across electrodes in the central brain region after the first week of treatment predicted later improvement in clinical scores [41].

While studies have analyzed the relationship between SSRI treatment and cordance for drugs such as escitalopram, venlafaxine, and bupropion, no studies to date have investigated the relationship between sertraline outcome and cordance and other EEG power measures. Earlier studies were further limited in their inclusion of relatively small sample sizes of subjects. Furthermore, including cordance as an EEG biomarker on top of power measures provides a larger, more cohesive understanding of how underlying electrical activity in the brain affects onset and outcomes of major depressive disorder. The findings of studies by Leuchter, et al and Hunter, et al show that EEG power measures can be used as biomarkers of MDD response. Importantly, such research provides some insight into the optimal treatment plan for patients

struggling with depression. Being able to determine the efficacy of a certain antidepressant based on an individual's EEG data allows for more personalized treatment and could significantly reduce the need for that patient to undergo various trials of pharmacological treatment before finding which would work best for them, which would be more time and cost-effective. Because the severity of MDD varies from patient to patient, establishing a more personalized treatment plan early on could increase the likelihood that a patient reaches remission sooner rather than later.

Therefore, taking inspiration from studies done by Leuchter, et al. and Hunter, et al., this project will process and analyze electroencephalography (EEG) and clinical data from the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study, in which 300 patients were enrolled, to determine if baseline or early changes in EEG power and cordance measures can predict sertraline outcome. Specifically, data analysis methods will be replicated from the aforementioned studies to determine if measures such as relative power, delta-theta/alpha ratio, or cordance are predictors of clinical outcome in a randomized, placebo-controlled sertraline trial for MDD.

# Methods

## 2.1 Data Collection

The Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study was funded by the National Institution of Mental Health (NIMH) and was completed over the course of five years from 2011 to 2016 [51]. It was a randomized, placebo-controlled clinical trial that investigated the ability of certain biomarkers to predict clinical outcomes in response to the commonly used the SSRI sertraline for MDD. Four different sites contributed to the collection and analysis of clinical, electroencephalography (EEG), and magnetic resonance imaging (MRI) data for 296 enrolled subjects: Columbia University Medical Center (CU), Massachusetts General Hospital (MG), University of Texas Southwestern Medical Center (TX), and University of Michigan (UM).

The primary inclusion criteria for this study consisted of those who were between the age 18-65, had a current diagnosis of nonpsychotic early onset, recurrent, or chronic MDD as determined by the Structured Clinical Interview for DSM-IV, had a Quick Inventory of Depressive Symptomatology - Self Report score of greater than or equal to 14, and had not failed any antidepressant trials in the current episode. The study was conducted in two stages, the first of which spanned eight weeks and investigated differences in treatment outcomes between sertraline and placebo treatment for MDD. The second stage also spanned eight weeks and explored the mediators of treatment outcomes between sertraline and bupropion. In this stage, responders from Stage 1 continued with their original randomly assigned treatment, while sertraline non-responders received bupropion and placebo non-responders received sertraline. Data from a healthy control group of 40 people, 10 from each of the four participating sites, were also collected.

The primary outcomes that were tested include symptom reduction, which was assessed using the HAMD, and treatment tolerability, which was assessed using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER). While clinical data from multiple surveys were collected periodically throughout each of the stages, neuroimaging data were collected only at baseline and the end of week one of the study [51]. Although EEG and MRI data were collected and made available for this dataset, only the EEG data will be considered for this project. Of the publicly available EEG data, only files for those subjects who had an EEG recorded at baseline and after one week of active or sham treatment were downloaded.

**2.2 EEG Data Preprocessing**

Prior to conducting data analysis, the EEG data needed to first be pre-processed. Raw EEG data in various formats (.bdf, .raw, .cnt) were downloaded from the online repository for the EMBARC study. Different research sites used different EEG technology to acquire the data and therefore had different raw file formats as well as a varying number of channels (between 64 and 128). Across all sites, EEG data were collected at baseline (pre-treatment) and after one week of active or sham treatment. Three of the four sites (MG, TX, and UM) acquired continuous EEG data at a sampling rate of 250 Hz while one site (CU) acquired data at a sampling rate of 256 Hz [52]. After downloading the data, EEGLAB, a program of MATLAB, was used to convert all the different formats into a .set file and all files were resampled at 250 Hz to create a uniform dataset [53]. For each of the subjects whose data qualified, their two EEG files were then combined into one larger .set file to allow for uniform processing at later steps. Finally, all combined .set files were re-referenced to the Fz electrode.

The next major pre-processing step was to run all files through Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER), a software embedded within

EEGLAB [54]. Each research site (CU, MG, TX, and UM) had a unique FASTER .eegjob file associated with it to account for the different number of channels, and all FASTER output files were referenced to the common average. After performing automated artifact rejection, the combined files were split back into individual files representing baseline and post one week of treatment. Next, only the channels common to all four sites, of which there were 55, were selected and .set files that only contained these channels were generated for analysis.

Then, a built-in function within EEGLAB, called ICLabel, was used to filter through the individual components of each of the files. Each individual component was classified as having some amount of 7 different classes of components: brain, muscle, eyes, heart, line noise, channel noise, or other, where brain components were given the label "1," muscle components were given the label "2," and so on [55]. The class with the highest numeric classification value in an individual component was then determined, and those components whose class label was "1," indicating it had the highest percentage chance of being brain, were kept while the remaining were rejected. After this step, the number of non-brain components in the file was calculated. Then, while iterating through all of the .set files, any that would not contain more than 5 individual components after rejecting the non-brain components were flagged as requiring manual visual inspection.

Next, the EEG power measures were obtained for each subject. The range for the individual frequency bands were defined as follows: delta (0.5-4 Hz), theta (4-8Hz), alpha (8-12Hz), and beta (12-20Hz). After calculating relative and absolute power for each of these bands and plotting the corresponding power spectrum at channels F3 and Oz, files were run through an algorithm which flagged certain subjects as requiring visual inspection if

- Any one of the following conditions were true: a greater than 1.5-unit difference between relative delta power and alpha power in Oz, more delta power than theta power in Oz, or more delta power than beta power in Oz **OR**
- Any one of the following conditions were true: a greater than 1.5-unit difference between relative delta power and alpha power in F3, more delta power than theta power in F3, and more delta power than beta power in F3 **OR**
- There was no significant IAF in Oz

Initially, for the first condition, simply specifying greater average delta power than alpha power led to files that did not have unwanted noise being flagged. Therefore, multiple modifications were tested before finalizing a 1.5-unit difference between relative delta and alpha power in Oz as the final condition. Assigning this numeric value resulted in only files whose power spectrums visually had high delta power, and subsequently unwanted noise, being flagged. Other relevant values that were calculated include the relative delta-theta/alpha power ratio at each channel, the mean relative delta-theta/alpha ratio across bipolar electrode pairs FPz-F7 and FPz-F8, and cordance in frequency bands delta, theta, alpha, and beta.

After all files were run through the visual inspection algorithm, those that were flagged were individually assessed by looking through all 55-channel data and deleting any epochs that had excessive noise or other significant artifacts. To ensure the commonly accepted adequate data length for EEG datasets in literature, any files that had less than 5 minutes of usable data were rejected entirely and removed from the file repository for further analysis. Some files showed significant eye or cardiac artifacts. For these files, individual component activations were plotted and those that resembled a pattern like the one present in the original file were removed manually, and then visual inspection was performed. Once visual inspection was

complete, the calculated power and cordance measures were extracted from each of the files. When calculating power, an FFT of 1000 data points was applied to 4 second epochs of data with a sampling rate of 250 Hz.

After quantifiable data had been extracted from the final subset of EEG files for the various subjects, the clinical data was downloaded and each patient's HAMD score at baseline and one-week post-treatment was extracted. Some patients that had EEG recorded at the two time points did not have a HAMD score recorded post one-week of treatment, so their clinical and EEG data were excluded for data analysis. Lastly, the files were sorted into those that received active treatment with sertraline (n = 86) and those that received sham treatment with a placebo drug (n = 92).

For cordance measures, data were collected from two montages: a 30-channel montage and an 18-channel montage (Fig. 1-2). These montages were generated based on 19- and 35-channnel montages defined in a cordance manual provided by the UCLA Department of Psychiatry and Biobehavioral Sciences, where the cordance measure was developed [42]. Some electrodes included in the original montages provided by this document were named differently in the EMBARC data and were substituted as such. For example, electrodes T3 and T4 from the original montage corresponded to electrodes T7 and T8 and electrodes T5 and T6 corresponded to electrodes P7 and P8. Any electrodes from the original montage that were not present in the EMBARC datasets were excluded from the montage. These electrodes included Cz, AF1, AF2, PO1, and PO2, of which Cz was excluded from the original 19-channel montage and all five of which were excluded from the original 35-channel montage.

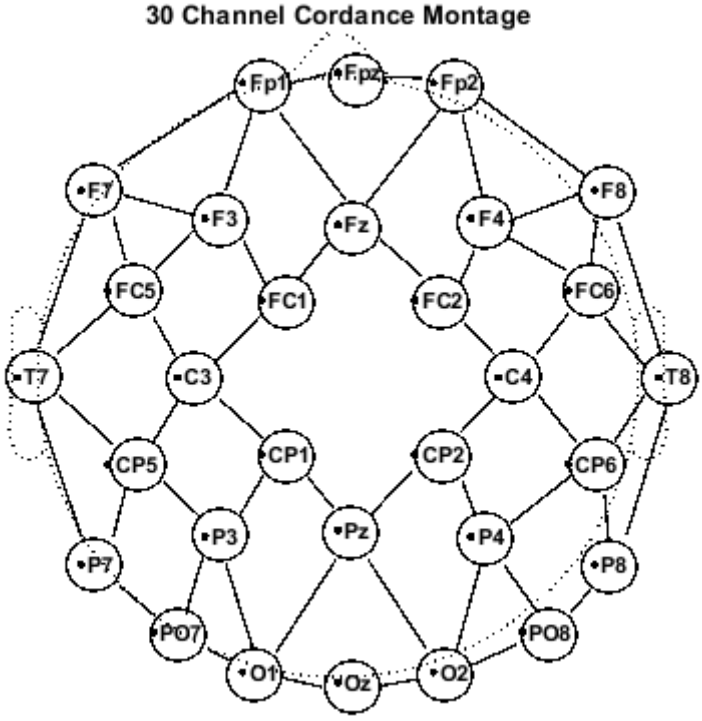


**Figure 1: 30 channel cordance montage**

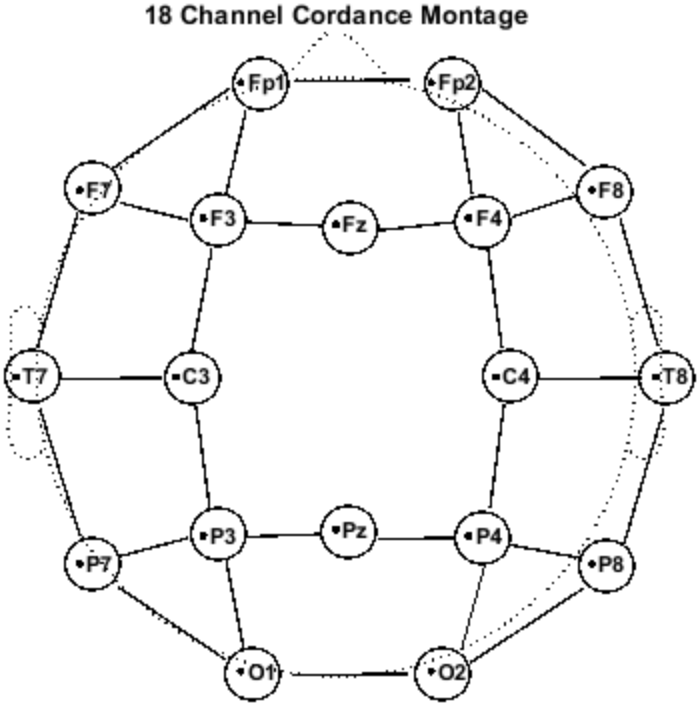


**Figure 2: 18 channel cordance montage**

## 2.3 Data Analysis

### *2.3.1 Statistical Analysis of Power and Ratio Measures*

Statistical analysis was conducted with the primary outcome of interest set to remission (HAMD score $\leq 7$) after 8 weeks of treatment as per Leuchter, et al 2017 [39]. First, within-group t-tests were done within the two treatment groups to determine if there was a significant difference between ratio measures at baseline versus Week 1. Then, a between-group t-test analyzed the average change in DT/A ratio across bipolar pairs FPz-F7 and FPz-F8 at Week 1 in the placebo versus sertraline groups. A chi-square analysis was also done to understand remission likelihood in the active and sham groups.

Once this initial statistical analysis was complete, binary logistic regression models were generated and receiver operator curve (ROC) analysis was conducted to evaluate early changes in DT/A ratio as a continued predictor of remission. In addition to these univariate regressions, multivariate logistic regression was performed while controlling for the effects of gender, age, baseline HAMD score, and baseline DT/A ratio as covariates. Finally, additional univariate binary logistic regressions were done using quartiles of average change in DT/A ratio values in the placebo and sertraline groups separately as predictors of remission likelihood. The percentage of remitters within each quartile was also calculated in conjunction.

### 2.3.2 Statistical Analysis of Cordance Measures

Next, statistical analysis was done using theta cordance in the 30-channel montage as a predictor of clinical response at Week 8 of treatment (HAMD $\leq 10$) according to methods outlined in Cook, et al [26]. Theta cordance was grouped by the following regions and averaged across the listed electrodes:

- Prefrontal: FP1, FPz, FP2

- Central: FC1, FC2
- Left temporal: T7, P7
- Right temporal: T8, P8

Once the data was separated by region, the subjects were then separated into four groups: placebo responders (P-R), placebo non-responders (P-NR), sertraline responders (S-R), and sertraline non-responders (S-NR). Theta cordance in the 30-channel montage was analyzed for group differences in the prefrontal, central, right temporal, and left temporal regions using separate one-way analysis of variance (ANOVA) (Fig. 3). For any regions that returned statistical significance ($p < 0.05$), t-tests and linear regression analyses were conducted.

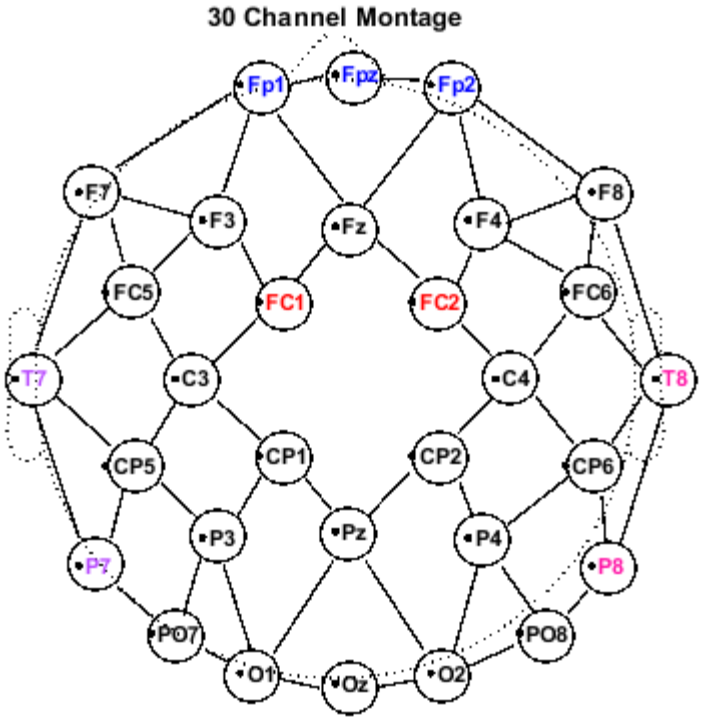


**Figure 3: Regional groupings of 30-channel cordance montage**
The regional groupings of the electrodes are labeled as follows:
blue = prefrontal, red = central, purple = left temporal, pink = right temporal

Finally, statistical analysis was carried out for theta cordance in the 18-channel montage (Fig. 4) as a predictor of treatment response (measured by a percent change in HAMD score ≥ 50%) as per methods outlined in Hunter, et al [41]. First, theta cordance values were grouped by region as follows and averaged to obtain one value for each subject:

- Prefrontal: FP1, FP2
- Midline-and-right-frontal: Fz, FP2, F4, F8
- Midline-and-left-frontal: Fz, FP1, F3, F7
- Central: Fz, C3, Pz, C4
- Midline-and-right-occipital: P4, O2, Pz
- Midline-and-left-occipital: P3, O1, Pz
- Occipital: O1, P3, Pz, P4, O2

After grouping the data, individual linear regression models were generated for average theta cordance across each region as single predictors of clinical response after 8 weeks of treatment. Then, any region that returned a significant overall model ($p < 0.05$) was further examined in a linear regression model that also controlled for age, gender, and baseline HAMD score. Significant regions were also examined with a linear regression model that used pretreatment baseline cordance as a single predictor of change in clinical outcome. Finally, any region that obtained statistical significance when using change in theta cordance as a predictor was evaluated in relationship to percent change in HAMD score from baseline to 2 weeks and 4 weeks after treatment using Pearson's bivariate correlation. These analyses were first carried out for the original 55-channel montage and were then replicated for the two additional montages. The same set of electrode groupings were used for these additional montages except for the 18-channel montage, which did not include FPz in any of the regions.

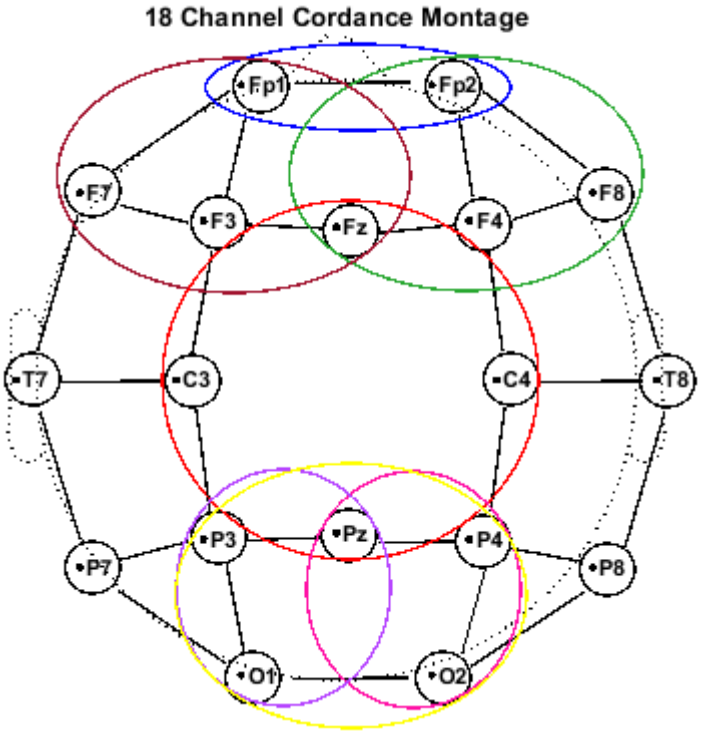


**Figure 4: Regional groupings of 18-channel cordance montage**
The regional groupings of the electrodes are labeled as follows: blue = prefrontal, green = midline-and-right-frontal, maroon = midline-and-left-frontal, red = central, pink = midline-and-right-occipital, purple = midline-and-left-occipital, yellow = occipital

# Results

## 3.1 Subject demographic and clinical characteristics

Clinical and demographic data for the placebo (N = 92) and sertraline (N = 86) treatment groups are presented in Table 1. Between placebo and sertraline remitters (HAMD $\leq$ 7 at week 8), age was the only variable that demonstrated significant difference ($p$ = 0.0426) [56]. Between remitters and non-remitters within the treatment groups, age ($p$ = 0.0211) and baseline HAMD score ($p$ = 0.0167) were found to be significantly different in the placebo group, but not in the sertraline group. Finally, remission rates were not significantly different ($p$ = 0.2) between the sertraline group (45.35%) versus the placebo group (35.87%).

| | Placebo (N = 92) | | | Sertraline (N = 86) | | |
|---|---|---|---|---|---|---|
| | **Remitters (N = 33)** | **Non-remitters (N = 59)** | **Statistical Difference ($p$-value)** | **Remitters (N = 39)** | **Non-remitters (N = 47)** | **Statistical Difference ($p$-value)** |
| Age (mean ± SD) | 32.39 ± 11.14 | 38.66 ± 12.88 | 0.02* | 38.64 ± 14.03 | 40.06 ± 14.83 | 0.65 |
| Gender (F:M) | 20:13 | 35:24 | 0.91 | 26:13 | 29:18 | 0.64 |
| Baseline HAMD (mean ± SD) | 17.18 ± 4.33 | 19.37 ± 4.02 | 0.02* | 17.87 ± 4.21 | 19.02 ± 4.73 | 0.24 |

*p < 0.05

**Table 1: Clinical and demographic characteristics for placebo and sertraline cohorts**

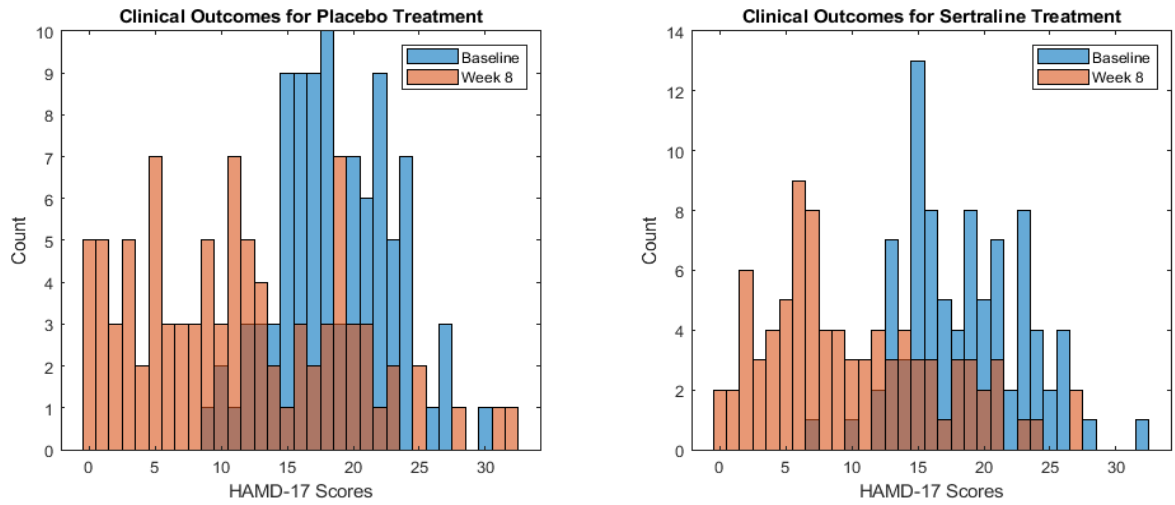


**Figure 5: Distribution of clinical HAMD-17 scores at baseline and Week 8 of treatment for placebo and sertraline cohorts**

### 3.2 Effect of placebo or sertraline treatment on DT/A ratio and the relationship between change in DT/A ratio and remission

We did not find any significant differences in Week 1 changes in the mean relative delta-theta/alpha (DT/A) ratio across FPz-F7 and FPz-F8 between placebo and sertraline groups. Between-group differences in the mean change in DT/A ratio or baseline DT/A ratio were also not significant. Binary logistic regressions showed that DT/A ratio was not a significant predictor of remission in the placebo nor sertraline groups. For the placebo group, the multivariate regression model examining gender, age, baseline HAMD score, and baseline DT/A ratio as covariates found age ($p$ = 0.0106) and baseline HAMD score ($p$ = 0.0113) as significant predictors of remission. None of the covariates were found to be significant predictors of remission in the sertraline group. A binary logistic regression analysis of DT/A ratio by quartile also did not return any significant results in neither group.

### 3.3 Change in theta cordance as a predictor of clinical outcome

#### *3.3.1 Regional theta cordance and response at Week 8*

Significant differences in change in theta cordance using the 30-channel montage between sertraline responders and non-responders were found at some electrodes (Fig. 6). While no statistically significant group differences were found within any of the four regions, change in theta cordance from baseline to Week 1 was significantly different between placebo responders and sertraline responders at electrode F8 ($p = 0.0338$) and between placebo non-responders and sertraline non-responders at electrode FC5 ($p = 0.014$). Due to a lack of significant findings in the regional analysis, no further statistical analysis was pursued using these parameters.

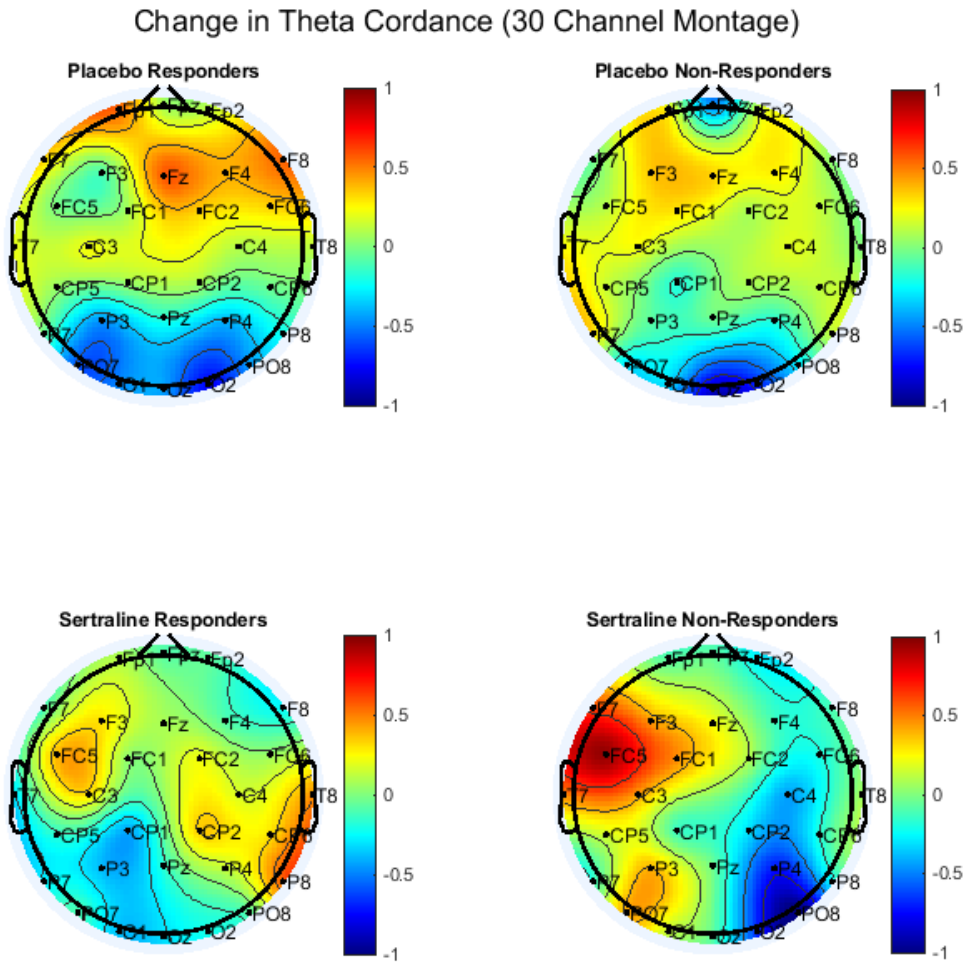


**Figure 6: Change in theta cordance (30-channel montage) after 1 week of treatment across responders and non-responders in placebo and sertraline group**

Using the 30-channel montage, no significant differences in theta cordance were found between placebo responders and non-responders. Between sertraline responders and non-responders, a significant difference was found in change in theta cordance after one week of treatment at electrodes T7 ($p$ = 0.0471), P3 ($p$ = 0.0329), P4 ($p$ = 0.0257), and PO8 ($p$ = 0.026).

### *3.3.2 Theta cordance and change in response from baseline to Week 8*

A significant difference in change in theta cordance using the 18-channel montage between sertraline responders and non-responders was found at one electrode (Fig. 7).

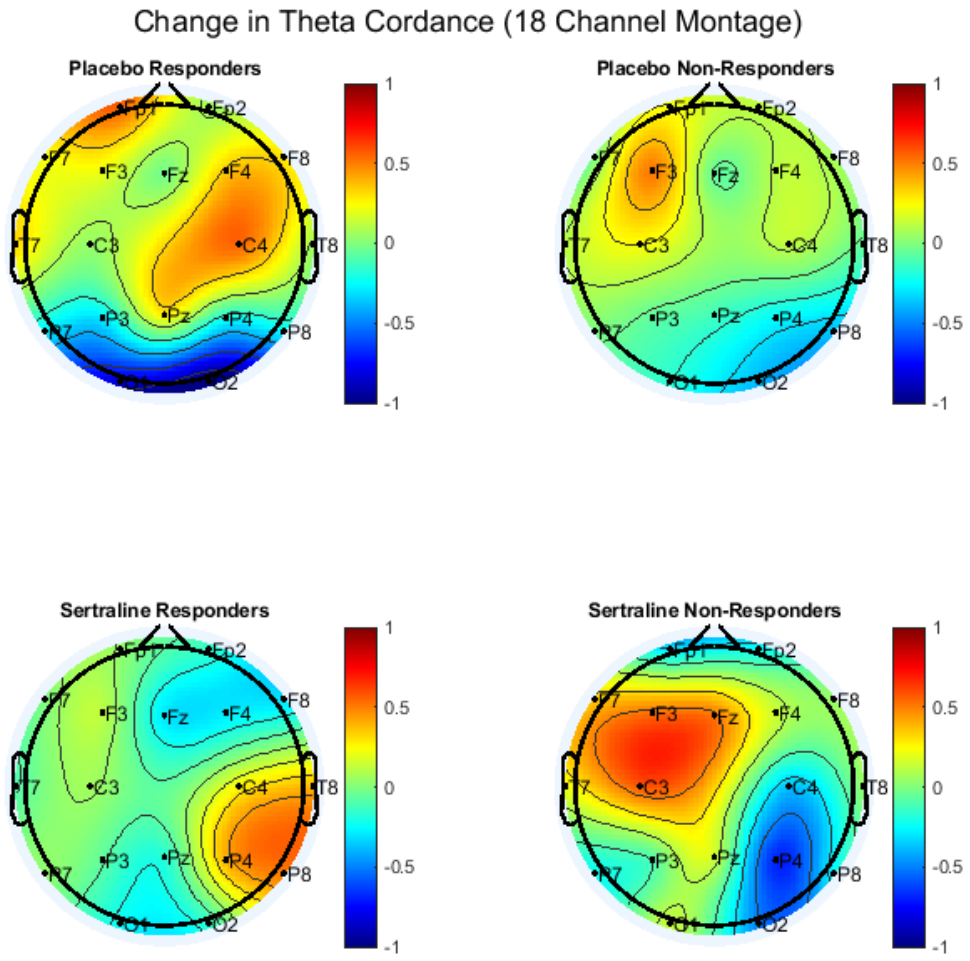


**Figure 7: Change in theta cordance (18-channel montage) after 1 week of treatment across responders and non-responders in placebo and sertraline group**
For this 18-channel montage, no significant differences in theta cordance were found between placebo responders and non-responders. Between sertraline responders and non-responders, a significant difference was found in change in theta cordance after one week of treatment at electrode P4 ($p$ = 0.0021).

Results from the linear regression analyses found that early changes in central theta cordance (CC) were significantly associated with percent change in HAMD score from baseline to Week 8 (Table 2). CC remained the only significant predictor of clinical response ($p$ = 0.0185) in a multiple regression model that controlled for age, gender, and baseline HAMD score as predictors. Trend-level significance was found when examining pretreatment baseline central

theta cordance as a single predictor of clinical outcome ($p$ = 0.092). As suggested by the results of the initial linear regression, there was a significant correlation between a decrease in central theta cordance and higher percent change in HAMD score (greater improvement) from baseline to Week 8 ($r$ = -0.2559, $p$ = 0.0174), but there was no significant correlation at Week 2 or 4.

| | **Outcome Measure: % Change in HAMD Score** | |
|---|---|---|
| **Regional qEEG Change in Theta Cordance After 1 Week of Treatment** | Placebo Treatment Group | Sertraline Treatment Group |
| PFC | p = 0.7656 | p = 0.307 |
| MRFC | p = 0.8464 | p = 0.0698 |
| MLFC | p = 0.1713 | p = 0.5521 |
| CC | p = 0.661 | p = 0.0174* |
| MROC | p = 0.8546 | p = 0.1807 |
| MLOC | p = 0.7537 | p = 0.4737 |
| OC | p = 0.8647 | p = 0.4172 |

Abbreviations: PFC, prefrontal; MRFC, midline-and-right-frontal; MLFC, midline-and-left-frontal; CC, central; MROC, midline-and-right-occipital; MLOC, midline-and-left-occipital; OC, occipital; HAMD, Hamilton Rating Scale for Depression 17-item
*p < 0.05; **p < 0.01

**Table 2: Statistical significance ($p$-values) of linear regression models analyzing relationship between early changes in theta cordance and clinical outcome**

## Discussion

The primary findings of this study posit evidence for treatment-emergent changes in theta cordance as a predictor of higher improvement in clinical scores for MDD patients treated with sertraline. In the given subset of the EMBARC study subjects, a decrease from baseline to Week 1 of treatment in theta cordance in the central brain region (CC) was associated with a greater percent change in HAMD score from baseline to Week 8 of treatment in sertraline-treated subjects, but not in placebo-treated subjects. When compared to clinical or demographic characteristics such as age, gender, and baseline depression severity, CC in the 18-channel montage remained the only significant predictor of treatment response. Data also suggested a trend, though not significant, between pretreatment baseline theta cordance and clinical outcome in the sertraline group. While these results do not perfectly replicate the Hunter, et al. finding of early changes in central theta cordance as a predictor of rTMS outcome, they demonstrate that the same biomarker could be used to predict sertraline outcome, which is important considering that antidepressants are often the first line of treatment for MDD patients. Furthermore, these findings warrant further research into the potential efficacy of pairing sertraline with rTMS treatment in order to improve MDD outcome. They further suggest that the underlying neurophysiological mechanisms of rTMS and sertraline treatment in depressed patients may share some similarities.

Although a previous study found that a change in the mean relative DT/A ratio was predictive of remission likelihood in the active but not sham treatment group, similar findings were not replicated in this dataset [39]. This discrepancy could be attributed to slight differences in the EEG preprocessing pipeline and stringent artifact rejection methods that were implemented for this dataset. Most notably, the original paper used a 35-channel montage with a

Pz reference while recording, while this dataset pulled a 55-channel data from differing size montages and re-referenced all data to electrode Fz. It is also possible that additional differences in the EEG recording protocol were present across the four different sites, which could have contributed to the introduction of unwanted noise.

Traditionally, manual visual inspection would ensure that the highest quality of EEG signal was preserved; however, this protocol was not practical given the number of subjects (200+) and length of recordings (~8-10 minutes). Therefore, automated artifact rejection was completed through FASTER, then individual component rejection was done using ICLabel, and finally the remaining files were automatically filtered for visual inspection based on spectral power distribution [54][55]. In each of these three steps, it is possible that built-in conditions to the programs are mistaking signal for noise and thus rejecting significant data. Generally, the main sources of noise in EEG signal originate near the frontal region of the brain, so automated removal of such noise may also be extracting signal that would be relevant to calculating a delta-theta/alpha ratio representative of that subject's data. In particular, removal of eye movement artifact, which is often picked up by prefrontal and frontal electrodes (such as FP1, FP2, F7, F8) and is usually reflected by high power in the lower end of the delta band, may be subsequently deleting important delta signal at the electrodes of interest.

When testing changes in theta cordance using a 30-channel montage as a biomarker of medication responders, the identification by several previous studies of early changes in average prefrontal theta cordance as predicting improved MDD outcome (HAMD $\leq$ 10) was not replicated [26]. Within-group t-tests at each electrode found significant differences in Week 1 change in theta cordance between sertraline responders and non-responders at several electrodes but no significant differences for the placebo group. However, further research would have to be

done to validate and confirm these findings. A number of previous studies have found that early changes in prefrontal theta cordance predict response to different antidepressant treatments, including fluoxetine, venlafaxine, citalopram, ketamine, rTMS, as well as to deep brain stimulation (DBS) and experimental antidepressant compounds but not to placebo [25][26][57][58][59]. It is not clear why this measure was not a robust predictor of response in these subjects, nor did it differentiate placebo from sertraline responders.

There are a number of factors that could contribute to the failure to replicate earlier studies. First, most studies examined medications other than sertraline. It is possible that EEG biomarkers developed on different medications or treatments are not applicable to sertraline, although previous research suggests that these biomarkers are independent of specific medication. Second, the current study used a different semiautomated pipeline for artifact identification and removal, in contrast to previous studies that relied primarily or exclusively on visual inspection to remove segments contaminated by artifact. It is possible that this new artifact removal technique also removed EEG activity of cerebral origin that was associated with differential treatment outcome. Next steps in this project will include reprocessing of the data using different strategies for artifact removal to determine if this yields different results. Third, it is possible that the absence of certain prefrontal electrodes (e.g., AF3 and AF4) in the EMBARC recording montage diminished the biomarker signal present in the EEG recordings. Next steps also include reanalyzing these data following interpolation of the missing electrodes. Additionally, five electrodes that were included in in the original study—AF1, AF2, Cz, PO1, and PO2—were not part of this study's 30-channel montage. Therefore, the connections surrounding the electrodes in the prefrontal region of the brain (FP1, FPz, and FP2) were very different, and this could have contributed to significant differences in the calculated average

prefrontal theta cordance values. Had the montages been the same, there may have been an association between prefrontal theta cordance and the sertraline responder group. Additionally, as was the case with the DT/A ratio protocol, qEEG data was collected using a Pz referential montage, which was not the case for this dataset.

## Limitations and Future Work

While this study's findings reflect a large sample size (N = 178) and a placebo-controlled dataset with which to compare findings, several limitations must be considered. Firstly, the lack of distinct clinical separation between the placebo and sertraline groups of this subset of subjects may have inherently limited any potential findings of neurophysiological differentiation between the two treatment groups. Furthermore, the original study used a 21-channel montage, while this study used an 18-channel montage. These differences likely contributed to a lack of significant findings or trends in other regions of the brain. In addition, the "central" electrode grouping implemented (Fz, C3, Pz, C4) varied slightly from that of the original study (Fz, C3, Pz, C4, Cz). It is possible that the inclusion of Cz in this dataset could have resulted in stronger associations not only with change in cordance as a predictor, but perhaps pretreatment baseline cordance as a predictor as well.

In order to test the previously identified potential sources of error, future work will first remove the condition regarding higher delta power than alpha power as implemented in the final flagging algorithm. If no prominent differences or trends are seen, changes will be made further back in the preprocessing pipeline, especially in FASTER and ICLabel, to simplify the artifact removal process through the implementation of less stringent conditions. Such modifications could help better understand the effects of each artifact removed within the different processing steps. Finally, implementing more or less dense cordance montages, defining different electrode groupings, or choosing different brain regions over which cordance was measured could result in more unique findings or biomarkers. These steps will bolster the initial findings of this study and allow for more robust conclusions to be made regarding other potential biomarkers of treatment outcome in MDD patients.

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