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Neurophysiological Characteristics of Magnetic Seizure Therapy vs. Electroconvulsive Therapy in Geriatric Patients with Severe Depression

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Neurophysiological Characteristics of Magnetic Seizure Therapy vs.
Electroconvulsive Therapy in Geriatric Patients with Severe Depression

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Master of Science Thesis

Neurophysiological Characteristics of Magnetic Seizure Therapy vs. Electroconvulsive Therapy
in Geriatric Patients with Severe Depression

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Abstract

Objective: Magnetic seizure therapy (MST) is under development as an alternative to electroconvulsive therapy (ECT), as it offers reduction in depression symptoms with fewer adverse cognitive effects. This study examined the feasibility and efficacy of MST versus ECT in a randomized trial of geriatric patients with severe depression, then compared the neurophysiological characteristics of seizures induced by MST or ECT and investigated potential links between seizure expression and therapeutic response.

Method: Six patients (mean age: 64.8) with severe depression were randomized to receive MST (n=3) or ECT (n=3) until maximal antidepressant effect (mean number of sessions: 14.67). Depression symptoms were assessed pre- and post-treatment using the Hamilton Rating Scale for Depression. Neuropsychological tests of verbal ability, visuospatial ability, memory, fluency, executive functioning, and motor functioning were administered pre- and post-treatment. 64-channel electroencephalogram (EEG) recordings were obtained at the start and end of treatment to capture power during ictal (seizure) and post-ictal periods for delta, theta, alpha, beta, and gamma frequency bands.

Results: Two ECT and three MST patients achieved remission of depression symptoms. EEG power and test performance did not differ between treatments. Ictal power and post-ictal suppression increased from the start to end of treatment in all frequency bands for the responders but not the non-responder. Increases in gamma ictal power and post-ictal suppression predicted slowing on a task of visuomotor skill and executive functioning, while increases in beta and theta ictal power and post-ictal suppression predicted improvement on a task of verbal fluency.

Conclusions: MST continues to show promise as an efficacious and feasible alternative to ECT. For both MST and ECT, increases in ictal power and post-ictal suppression in all frequency bands may be indicators of treatment response, and associated with impairments to visuomotor functioning.

Keywords: Electroconvulsive therapy, magnetic seizure therapy, EEG, ictal power, post-ictal suppression

Introduction

Electroconvulsive therapy (ECT) has long been established as an efficacious treatment for severe depression (Engel & Kayser, 2016; Kho, van Vreeswijk, Simpson, & Zwinderman, 2003). With a 60% remission rate in adults with depression and about a 50% response rate for treatment-resistant depression, ECT is at least as equally effective as antidepressant medications, especially for individuals who have undergone multiple medication trials without success (Blumberger, Hsu, & Daskalakis, 2015). Geriatric patients are preferentially referred for ECT over younger patients, perhaps due to intolerance to antidepressants, histories of treatment non-response, and greater probability of having cardiovascular diseases (Dombrovski & Mulsant, 2007). Not only is ECT considered safer than medication in regards to cardiovascular risk, but there is evidence that ECT is more effective than pharmacotherapy alone in depressed geriatric patients (Philibert, Lynch, & Winokur, 1995).

During ECT, small electric currents are passed through the skull and into the brain of the anesthetized patient in order to trigger a brief seizure. Despite strong support for its efficacy, a major concern regarding ECT is its adverse cognitive effects, which impact more than 40% of patients (Engel et al., 2016). These adverse effects include disorientation lasting up to 40 minutes, retrograde and anterograde amnesia, difficulty concentrating, and slowed processing (Dybedal, Tanum, Sundet, Gaarden, & Bjølseth, 2014). The severity of these cognitive effects has been associated with advancing age, which is especially relevant to the depressed geriatric population (Sackeim et al., 2007). There is ongoing debate regarding the chronicity of ECT's adverse effects, where one systematic review reported no long-term adverse cognitive effects lasting more than six months following treatment (Kumar et al., 2016), while another study reported slowed reaction time and impaired memory at six month follow-up (Sackeim et al.,

2007). Nevertheless, anecdotal evidence of permanent memory loss raises concerns among potential patients.

Magnetic seizure therapy (MST) is under development as an alternative to conventional ECT in the treatment of severe depression. MST uses high frequency repetitive transcranial magnetic stimulation (rTMS) to induce seizures. A coil placed near the patient's head generates a magnetic field that can pass through the scalp and skull to induce a small electric current in the brain. In 2008, rTMS at low frequencies was approved in the U.S. as treatment for depression in medication non-responders up to 69 years old (NIMH, 2016). rTMS reduces depressive symptoms with only transient discomfort during stimulation and no cognitive effects (Blumberger et al., 2015; Loo & Mitchell, 2005). However, its efficacy is lower than that of ECT (George et al., 2010), and there is little evidence of its efficacy specifically in geriatric populations. By using higher frequencies of stimulation (> 50 Hz), MST may amplify the antidepressant effect of rTMS by inducing a seizure similarly to ECT. The development of MST aims to combine the lower side effect profile of rTMS with the efficacy found from seizure induction in ECT.

In developing and testing MST, both its efficacy and adverse effects must be considered and balanced to determine its feasibility as an alternative treatment. In ECT, efficacy and side effects are both influenced by the site of seizure induction and the extent of stimulation (Sackeim et al., 2008), which are difficult to control using conventional ECT protocol. There is ongoing debate regarding the parameters of ECT administration that would best maintain efficacy while minimizing side effects, such as number and location of stimulation sites, and the importance of

individual seizure thresholds (Abrams, 2002). However, since the skull has a high impedance, it shunts electrical current through the scalp and cerebrospinal fluid surrounding the brain, resulting in widespread stimulation of cortical and subcortical regions regardless of ECT configuration (Cretaz, Brunoni, & Lafer, 2015). A simulation study showed that standard ECT configurations can stimulate up to 94% of brain volume at a suprathreshold level, with the hippocampus being exposed to stimulation in all ECT configurations (Lee, Lisanby, Laine, & Peterchev, 2016). Subcortical and hippocampal activation during ECT is thought to contribute to its cognitive side effects.

By contrast, MST uses magnetic stimulation that bypasses the skull, which avoids the issue of skull impedance and shunting, thus offering better control over the spatial distribution of stimulation (Cretaz et al., 2015). Both simulations and intracerebral recordings have shown that MST induces less intense electric fields that are more confined to superficial cortex (Hoy & Fitzgerald, 2011; Lee et al., 2016; Lisanby, Luber, Schlaepfer, & Sackeim, 2003). With more confined stimulation, MST offers reduced risk of hippocampal activation, which may result in fewer memory-related side effects.

The first MST device was a custom rTMS machine and was tested in preclinical trials in 2000, followed by the first human test in 2001, which resulted in a reduction in depression score (Lisanby, Schlaepfer, Fisch, & Sackeim, 2001). Since then, several open-label studies have demonstrated the efficacy of MST and that its antidepressant response was comparable to that of ECT (Kayser et al., 2011, 2015; Kosel, Frick, Lisanby, Fisch, & Schlaepfer, 2003). In addition, MST resulted in fewer cognitive side effects and faster reorientation than ECT (Cycowicz,

Luber, Spellman, & Lisanby, 2009; Kayser, Bewernick, Hurlemann, Soehle, & Schlaepfer, 2013; Lisanby et al., 2003; Moscrip, Terrace, Sackeim, & Lisanby, 2006). Therefore, MST shows promise as an efficacious alternative to ECT. However, the mechanism by which they elicit therapeutic response is still unclear, though there are several hypotheses, including localized suppression of neural metabolic activity, adaptive changes in monoamine neurotransmitter systems, regulation of the hypothalamic-pituitary-adrenal axis, and influences on neural plasticity and neurogenesis (Charney, Menkes, & Heninger, 1981; Merkl, Heuser, & Bajbouj, 2009; Sackeim, Decina, Prohovnik, Malitz, & Resor, 1983).

Examining characteristics of the seizures induced by ECT and MST may improve understanding of their therapeutic mechanisms by pinpointing properties correlated with antidepressant response. Electroencephalography (EEG) can be used to measure electrical brain activity at the scalp level before, during (ictal), and after (post-ictal) seizures. Studies of simultaneous EEG-ECT have shown that greater total ictal power, delta power, and post-ictal suppression, the difference between ictal and post-ictal power, are predictive of better response to treatment (Luber et al., 2000; Mayur, 2006; Nobler et al., 2000; Perera et al., 2004). When comparing the neurophysiological characteristics of MST and ECT using two-channel EEG in non-human primates, ECT resulted in significantly greater ictal power and post-ictal suppression for all frequency bands compared to MST (Cycowicz et al., 2009; Lisanby et al., 2003). However, these differences may have been due to limitations of the MST and recording equipment, and it is unknown whether the association between ictal power, post-ictal suppression, and therapeutic response adheres for MST in humans as well. It may not be necessary to induce as intense of an electric field or seizure using MST in order to elicit therapeutic effects. In fact, a reduced electric

field may be advantageous in that the current and the seizure would stay confined to superficial cortex, reducing the likelihood of generalization to limbic structures involved with memory.

Further exploration of the differences in ictal and post-ictal expression between MST and ECT and their relation to treatment response may clarify mechanisms of therapeutic action in induced seizures, and identify seizure parameters to be optimized for efficacy.

Though general neurophysiological characteristics of ECT have been identified, EEG research in brain stimulation therapies has thus far been limited by technological challenges. Most EEG studies (Lisanby et al., 2003; Cykowicz et al., 2009) have used passive electrodes, which have no built-in circuitry and are therefore better able to withstand currents applied from ECT or MST. However, it is difficult to detect smaller signals with passive electrodes than with active electrodes, which have built-in circuitry to amplify the signal even before it reaches the amplifier, thereby improving signal quality dramatically. The downside of active electrodes used to be their dysfunction when subjected to high input from ECT, MST, or TMS, but that has been resolved in recent iterations of more durable active electrode caps. Unlike past comparisons of MST and ECT that used two-channel passive caps, the current study uses a 64-channel active cap. Recording with a high-density active cap not only results in better signal quality, particularly for low-amplitude high-frequency oscillations, but it can also show differential ictal expression from different brain regions.

The current study of MST and ECT has two major goals: First is to evaluate the feasibility and antidepressant efficacy of MST in elderly patients with severe depression. We hypothesize that MST will result in a significant decrease in depressive symptoms. Demonstrating the usability of

MST would further its development as a safer and more favorable alternative treatment to conventional ECT. The second goal of the current study is to compare the neurophysiological characteristics of MST and ECT in human patients. In line with findings in non-human primates, we expect that MST will show lower ictal power and therefore less post-ictal suppression. To date, this is the first simultaneous high-density EEG-MST study in humans using an active cap. Investigating both treatments through high-density EEG may provide insight into the mechanisms by which elicited seizures result in differing therapeutic response in depressed patients.

Methods

This study was approved by the New York State Psychiatric Institute (NYSPI) Institutional Review Board.

Participants

Fifteen eligible individuals enrolled in the study and began treatment. Two participants withdrew from the study prior to completion. Complete sets of EEG recordings were obtained for eight participants. Two participants' data were omitted from analyses due to issues with recording. Of the remaining six participants, five were female. The six participants ranged in age from 57 to 74 years old (mean: 64.8, standard deviation [SD]: 7.41, Table 1).

All participants were between the ages of 55 and 90 and willing and capable of providing informed consent. Participants were recruited via flyers and brochures at NYSPI, as well as referral by private physicians and clinical services at NYSPI and other psychiatric facilities.

Participants were eligible to participate if they had received a clinical diagnosis of a major depressive episode in the context of unipolar or bipolar disorder, a Hamilton Rating Scale for Depression (HRSD) score ≥ 20 (indicating severe symptoms of depression), and a Mini Mental State Exam score ≥ 24 (indicating normal cognition). Outpatients enrolling in the study needed to be living with a responsible adult to provide support and oversee treatment adherence.

Participants were excluded if they had a history of schizophrenia, schizoaffective disorder, rapid cycling bipolar disorder, or substance abuse or dependence within the last three months as determined by the Structured Clinical Interview for Diagnosis (SCID-IV) and a urine toxicology screen. Participants were also excluded if they had a current unstable or serious medical condition, or any medical condition that substantially increased the risks associated with MST or ECT as determined by physician evaluation. Participants with a history of neurological disorder, epilepsy, stroke, brain surgery, metal in the head, known brain lesions, or moderate to severe head trauma were excluded due to potential risks associated with MST and ECT. The presence of devices that may be affected by MST or ECT (e.g. pacemakers, cochlear implants, implanted brain stimulators, and intracardiac lines) was also a contraindication to treatment. Patients who had a history of ECT treatment within the past six months or who had failed to respond to a past adequate trial of ECT were excluded as well.

Procedure

Eligible participants were randomized to receive magnetic seizure therapy (MST) or electroconvulsive therapy (ECT) treatment. Of the participants included in later analyses, three received MST and three received ECT. They were masked to which treatment they received.

Participants assigned to ECT completed a physical exam, blood work, and received medical clearance in accordance with the NYSPI Policy and Procedure Manual for ECT.

Psychotropic medication washout: In order to determine the efficacy of MST and ECT in the absence of additional treatment, all participants were washed out from psychotropic medications for five days prior to treatment with the exception of lorazepam up to 3mg/day. Leading to the washout period, each participant received a schedule for tapering medications tailored to their regimen and clinical status.

Motor threshold and seizure titration: To determine the intensity of subconvulsive repetitive transcranial magnetic stimulation (rTMS) necessary for MST, motor threshold and seizure threshold were obtained on the first and last treatment sessions. Motor threshold was defined as the minimum magnetic flux necessary to elicit a 50-microvolt peak to peak electromyography (EMG) response in five out of ten trials when administering single pulse TMS to the contralateral primary motor cortex. Seizure threshold was determined using the stimulus titration and ascending method-of-limits procedure, where increasingly powerful stimuli were applied until a seizure of adequate duration (≥ 20 seconds) was induced.

Anesthesia: Prior to treatment, all participants were given atropine (0.4 mg i.v.) to prevent post-seizure bradycardia, general anesthesia, and succinylcholine (0.75-1.0 mg/kg) as an intravenous muscle relaxant. Seizure duration was monitored via EEG and motor manifestations. A blood pressure cuff was placed and inflated on a limb prior to succinylcholine administration to prevent

exposure to the muscle relaxant to that limb, thus allowing observation of the motor seizure while reducing risk of injury.

Magnetic seizure and electroconvulsive therapy: MST was administered bilaterally using a MagPro coil with simultaneous stimulation over the left dorsolateral prefrontal cortex and to the right of vertex at 5x seizure threshold (MagVenture A/S, Farum, Denmark; 50 Hz, biphasic, 370 μ s phase width). Seizure threshold was typically reached at 200 pulses, so that treatment dosage was 1000 pulses on post-titration treatment days. ECT was right unilateral at 5x seizure threshold (Thymatron ECT Machine, Somatics, LLC, Lake Bluff, IL; Ultrabrief stimulus – 0.25-0.3ms). Treatments were administered three times per week, with the number of sessions ranging from 8 to 18 for participants who completed the study (mean: 14.67, SD: 3.78, Table 1). Treatment was terminated at maximal antidepressant effect, when participants reached their lowest score of depressive symptoms on the HRSD or showed no further improvement over three subsequent treatment sessions. Participants that did not show a clinically significant decline in depressive symptoms were offered standard-of-care inpatient clinical treatment at no cost, as determined by discussion with their providers.

Measures

Clinical Ratings

The primary clinical outcome measure was the 24-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Typically, scores of 20 or higher on the HRSD are considered indicative of moderate to severe depression, while scores in the 0-7 range are considered normal. HRSD scores were obtained through clinician rating at baseline prior to treatment and within

seven days after the last session. Response to treatment was indicated by a > 50% decrease in HRSD score, while remission was indicated by a > 60% decrease or a post-treatment score in the normal range.

Neuropsychological Assessment

Participants completed a neuropsychological battery prior to treatment and within seven days of the last session. The battery included measures of verbal ability, visuospatial ability, memory, fluency, executive functioning, and motor functioning. The extended 57-point Mini Mental State Exam (MMSE) was administered to assess general cognitive impairment (Stern, Sano, Paulson, & Mayeux, 1987). The Wide Range Achievement Test (WRAT) was used to assess verbal and mathematical ability, specifically the ability to read words, comprehend sentences, spell, and perform calculations (Wilkinson & Robertson, 2006). The Rey-Osterrieth Complex Figure Test (ROCF) was used to assess visuospatial reasoning, memory, and organization (Rey, 1941).

Participants were asked to recreate a complex line drawing first by copying it and then by memory. The Buschke Selective Reminding Test, Goldberg Remote Memory Test, and Autobiographical Memory Index (AMI) were used to assess short-term and long-term memory storage and retrieval, as they evaluate recall of spoken words, famous people and events, and diverse personal events, respectively (Buschke, 1973; Goldberg, 1985; Sackeim et al., 1993). Digit Span Total, the sum of forward and backward, was used to assess working memory, where participants recalled sequences of digits in the order they were presented and in reverse order (Wechsler, 2014). The Controlled Oral Word Association Test (COWAT) and the Category Fluency Test were used to assess verbal fluency, where participants were asked to name as many words starting with a certain letter or belonging within a certain category as possible within a set

time period (Ruff, Light, Parker, & Levin, 1996; Lezak, Howieson, & Loring, 1995). The Stroop task (word only, color only, and color word conditions) was used to assess processing speed and executive functioning (Lezak et al., 1995). Participants read color words, named the color of the ink neutral words were printed in, and named the color of the ink of incongruent color words.

The Trail Making Test was used to assess visuomotor and executive functioning, where participants first connected letters in order that were distributed across the page (Trails A: A, B, C, etc.). Then, they connected letters and numbers in alternating sets (Trails B: 1, A, 2, B, etc.) using a single trace (Lezak et al., 1995). The B/A ratio of scores on the Trail Making Test was used to assess executive functioning beyond the effects of visuomotor skill and search speed (Martin, Hoffman, & Donders, 2003). The Grooved Pegboard Test was used to assess motor dexterity in both the dominant and non-dominant hand, where participants inserted keyed pegs into holes with randomly positioned slots (Roy & Square, 1994). The Buschke Selective Reminding Test and the ROCF were omitted from analyses due to invalid or missing data.

Electroencephalography: Electroencephalograms (EEG) serve as indirect measures of electrical activity from the brain taken at the scalp level. Recordings were obtained at the first session post-titration (start) and penultimate or last (end) sessions (BrainAmp MR plus amplifiers with EasyCap, BrainProducts GmbH, Gilching, Germany). 64-channel EEG was obtained during the treatment period, as well as during eyes open and eyes closed resting conditions 15 minutes prior to and 15 minutes following treatment (sampling rate: 500Hz, low cutoff: 0Hz, high cutoff: 250 Hz, online reference electrode: Fpz, ground electrode on left mastoid, no dedicated EOG channels).

EEG Pre-processing

64-channel EEG recordings from during treatment sessions were analyzed using BrainVision Analyzer 2 (BrainProducts GmbH, Gilching, Germany). Recordings were first visually inspected for channels that stopped recording or showed excessive artifacts, which were removed from further analysis. Two of eight participants were removed from analysis at this point due to recording errors that resulted in the omission of ictal or post-ictal periods. When fewer than six channels needed to be removed and they were distributed across the scalp, they were instead interpolated as recommended by Picton et al. (2000) using the spherical splines method (Perrin, Pernier, Bertrand, & Echallier, 1989). All remaining channels were then average referenced and put through a band-pass filter (0.4-100Hz with 12dB/octave rolloff). Eye blinks and movement were attenuated using ocular correction independent components analysis. Artifacts were automatically marked on individual channels following pre-set criteria: 50 $\mu\text{V}/\text{ms}$ maximal gradient, 400 μV in 200ms maximal difference, -300 to 300 μV amplitude variation, and 0.5 μV for 100ms minimal activity. The gradient criterion marked large differences between consecutive sampling points, the difference criterion marked large differences between minimum and maximum within a sliding window segment, the amplitude criterion marked extreme amplitude values, and minimal activity marked very low differences between minimum and maximum values within a segment. In combination, these artifact detection criteria ensured that non-recording electrodes and noise from movement, muscle contractions, or electrical interference did not affect further analyses.

Ictal and post-ictal start and end markers were placed according to visual inspection. The ictal period was defined as the period immediately following ECT or MST stimulation until the end of

seizure activity as observed in the EEG. Motor observations of seizure duration were used to guide marker placement. Two post-ictal periods were defined as the two subsequent 10-second periods following the ictal period.

EEG Analysis

The first 10 seconds of the ictal period were extracted for equivalent duration to the post-ictal periods. 10 frontal channels were analyzed, five on the left (AF3, F1, F3, F5, FC3) and five on the right (AF4, F2, F4, F6, FC4) (Figure 1). Previously marked artifacts in the frontal channels were removed by setting waveform values during the artifact to the value immediately preceding the artifact in order to produce a flat line with zero slope. All values following the artifact were then shifted to connect to the new value at the end of the artifact. Though this method is not commonly used in EEG analysis, it avoids false artifacts that would arise from cutting out artifacts and splicing together the remaining data, as well as a false low-frequency signal that would arise from connecting the remaining data with a sloped line.

Ictal and post-ictal periods underwent a 60 Hz notch filter, then a Morlet wavelet transform in a custom MATLAB script (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007) to determine average power within each of five frequency bands (delta: 0.5-4 Hz, theta: 4-8 Hz, alpha: 8-12 Hz, beta: 14-28 Hz, gamma: 30-58 Hz). Power values of zero obtained from artifact removal were excluded from the averaging, as well as power values greater than two standard deviations away from the mean for each frequency band. The Morlet wavelet function is a transformation that decomposes the EEG signal into its constituent frequency components while maintaining the time domain, unlike fast Fourier transforms (Grossmann & Morlet, 1984). These frequency

components can then be grouped into bands and their power analyzed at different time points or averaged across a specified period for each channel. This analysis resulted in average power values for five frequency bands for each of ten frontal channels within three periods (ictal, post-ictal 1, and post-ictal 2). These average power values were calculated for each participant at their start and end treatment sessions.

Power was averaged across channels within each hemisphere, then the hemispheres were averaged to obtain power values representative of frontal EEG. Post-ictal suppression was calculated as the difference in power between the ictal period and the first post-ictal period. To assess change in EEG across the course of treatment, differences in ictal power and post-ictal suppression between the start session and the end session were calculated.

Statistical Analysis

A repeated-measures ANOVA was used to assess the main effects and interactions of treatment, session, period, and hemisphere on power (afex, R package version 0.16-1, 2016). Hemisphere (left or right), session (start or end), and period (ictal, post-ictal 1, or post-ictal 2) were within-subjects factors while treatment (MST or ECT) was the between-subjects factor. Post-hoc analyses assessed the direction of main effects and interactions between factors (lsmeans, R package version 2.26-3, 2016).

Since treatment termination was determined by decrease in HRSD score, treatment duration varied by participant. Pearson's correlation analyses assessed the relationship between the number of treatments and changes in ictal power and post-ictal suppression for the five frequency bands.

To examine the relationship between EEG characteristics and performance on neuropsychological tests, hierarchical/sequential multiple regression analyses were used. Test performance was first regressed only on treatment (Model 1), then on treatment and change in ictal power (Model 2a), or treatment and change in post-ictal suppression (Model 2b). ΔR^2 from Model 1 to Model 2 indicated the increased fit of the regression model when considering change in ictal power or post-ictal suppression after controlling for treatment. Model 2 analyses with $\Delta R^2 > .7$ were investigated further. Finally, the interaction between treatment and change in ictal power (Model 3a) or change in post-ictal suppression (Model 3b) was added to each respectively.

Results

Five (2 ECT, 3 MST) of six patients responded to treatment and achieved remission of depression symptoms as indicated by >60% decrease in HRSD score (Table 1). MST responders showed a range of 13 to 18 treatment sessions, while ECT responders showed a range of 16 to 18 sessions. Neither treatment nor the number of treatment sessions predicted change in ictal power or change in post-ictal suppression for any of the frequency bands.

Power did not differ between left and right hemispheres and hemisphere did not interact with other factors, so power was averaged across hemispheres for the following analyses. The effects of treatment, session, and period on average frontal power within the five frequency bands for the five responders were assessed using a repeated-measures ANOVA (Table 2). Power did not differ by treatment for any of the frequency bands. Power differed by session for theta and alpha, where the end session showed higher power on average than the start session. Though power did not significantly differ by period, power during the ictal period tended to be higher than during

either of the post-ictal periods (Figure 2). There was a significant interaction between session and period for delta, theta, and alpha bands. Post-hoc analyses indicated that the ictal power was higher during the end session than the start session, while post-ictal power did not differ across sessions (Figure 2). By contrast, the non-responder did not show as marked post-ictal suppression or an increase in ictal power for the end session.

Neuropsychological assessment

Model 1 of hierarchical regression analyses regressed change in test performance from start to end session on treatment. Treatment did not significantly predict change in test performance for any tests. Models 2a and 2b predicted test performance from treatment and change in ictal power or change in post-ictal suppression, respectively. Neither change in ictal power nor post-ictal suppression predicted change in performance on the Goldberg Remote Memory Test, the Category Fluency Test, Digit Span, the Autobiographical Memory Index, or the Stroop task, after controlling for treatment

However, change in ictal power or post-ictal suppression did contribute to change in Trails, COWAT, and Grooved Pegboard performance. An increase in gamma ictal power or post-ictal suppression significantly predicted an increase in Trails B/A ratio after controlling for treatment (Table 3, Model 2; Figure 3). Since the Trails B/A ratio represents executive functioning in switching sets, an increase in the ratio indicates slowing of cognitive functioning. Thus, larger increases in gamma ictal power and gamma post-ictal suppression across the course of treatment were associated with greater impairment of executive functioning.

An increase in beta ictal power or post-ictal suppression also significantly predicted an increase in COWAT score after controlling for treatment (Table 4, Model 2; Figure 4). An increase in

theta post-ictal suppression significantly predicted an increase in COWAT score after controlling for treatment, and there was a trend towards an association between an increase in theta ictal power and COWAT score (Table 5, Model 2; Figure 5). An increase in COWAT score indicates improved performance, so increased theta and beta ictal power and theta post-ictal suppression were associated with improvements in verbal fluency.

An increase in alpha ictal power may be associated with an increase in Grooved Pegboard Non-dominant score (Table 6, Model 2a; Figure 6), where an increase in score indicates slowing in motor performance. The interaction between treatment and change in ictal power or post-ictal suppression did not contribute to any of the models generated. Therefore, treatment did not moderate the effect of ictal power or post-ictal suppression on cognitive performance.

Discussion

This study presents the first human neurophysiological findings using high-density EEG comparing ECT and MST for the treatment of severe depression. The primary finding of this study involved the differential pattern of ictal expression across the course of treatment between the responders and the non-responder. All patients showed increased power during the ictal period than the post-ictal periods, though the small sample size limited statistical significance. However, ictal power and post-ictal suppression were markedly larger for the responders in all frequency bands. An interaction between session and period in the responder group indicated a change in the seizure characteristics across the course of treatment, where seizures at the end of treatment showed greater power and larger post-ictal suppression than at the beginning of treatment. This change across treatment was not seen in the non-responder, which suggests that an increase in ictal power and a corresponding increase in post-ictal suppression may be linked to therapeutic response. Such a link between global ictal power and post-ictal suppression,

particularly in the delta band, with therapeutic response has been found in the ECT literature, but has not yet been generalized to MST or other frequency bands (Engel et al., 2016; Mayur, 2006). By using an active cap to record quality signal in frequencies up to 60Hz, this study found patterns of increasing ictal power and post-ictal suppression in higher frequencies as well as in MST.

Of the six patients with complete data, all of the three MST patients obtained remission of depression symptoms within 18 sessions, which was a treatment duration similar to that of ECT response in this study. However, a study of ECT in the elderly reported a mean of 7.3 sessions to reach remission and typical ECT treatment courses are only 8-12 sessions (Blumberger et al., 2015; Engel et al., 2016). The longer treatment duration of this study was likely due to the termination criteria of maximal antidepressant effect such that patients could have met criteria for remission, then continued to show reduction in depression symptoms for several sessions before treatment termination. Nevertheless, these results support the antidepressant efficacy of MST in comparison to ECT in a randomized trial.

In contrast to past research, MST and ECT did not differ in terms of power in either the ictal or post-ictal periods. Non-human primate and human studies have found that MST results in lower ictal power and less post-ictal suppression than ECT (Cycowicz et al., 2009; Lisanby et al., 2003). However, recent development of the MST equipment has allowed for greater output intensity such that the energy multiplier of the seizure threshold used in MST stimulation more closely resembles that of ECT. Therefore, differences in ictal power in past literature may have reflected limitations of MST technology at the time. MST and ECT also did not differ in terms of their effects on cognitive functioning.

Change in ictal power and post-ictal suppression across the course of treatment were linked to changes in cognitive functioning, though the relationships differed between domains of functioning. Increases in ictal power and post-ictal suppression were linked to slowing on Trails and Grooved Pegboard, but an improvement in the COWAT. An improvement in neuropsychological functioning post-treatment was found in another randomized trial of MST vs. ECT with medium effect sizes for measures of visuospatial learning, but there was a slight decline in performance for verbal fluency (Kayser et al., 2015). The improvements in cognitive functioning may have been due to a reversal of baseline cognitive deficits associated with severe depression. The differences in performance found in this study do not closely replicate those found by Kayser et al. (2015), but they may be explained in terms of the particular domains of functioning adversely affected by treatment. Though the second portion of the Trail-Making Test assesses the ability to alternate sets and monitor performance, it also relies heavily on visual search and visuomotor skills. The ratio score for Trails is meant to account for the effect of motor functioning as it considers performance on a simpler visual search task, but it does not account for the increased demand on visuomotor skills given the larger number of potential targets to search through and connect. Performance on the Grooved Pegboard test also relies heavily on visuomotor skills. As the COWAT is administered orally, it does not require any visual or motor responses. The difference in association between ictal power or post-ictal suppression and cognitive functioning may reflect treatment's specific effects on visuomotor functioning while verbal fluency and other aspects of executive functioning are preserved or improved.

Though this study presents new findings regarding potential neurophysiological characteristics of therapeutic response to MST, these results are subject to limitations. Sample size was a major

limitation to interpreting results involving differences between treatments. Based on estimated small effect sizes between MST and ECT, power analyses indicated that a sample size of seven per group would be necessary to better assess the effects of treatment and period on power (G*Power, Version 3.1, 2014). Lack of an MST non-responder was another limitation, as a non-responder for comparison to the responder group would provide further evidence to whether the relationship between therapeutic response and ictal power and post-ictal suppression applies to MST as well as ECT.

Additional studies should continue to examine neurophysiological characteristics associated with therapeutic response in MST, and to what extent these relationships match those found in ECT. Specifically, though this study suggests a general association between higher ictal power and post-ictal suppression with treatment response, evidence for that link in MST is scarce. It is also unclear whether the same degree of ictal power and post-ictal suppression as seen in ECT is necessary for equivalent treatment outcomes. Understanding the neurophysiological characteristics of seizures linked to treatment response would aid the optimization of ECT and MST parameters for efficacy.

To present a comprehensive picture of MST as an alternative treatment to ECT for depression, side effect profiles, particularly cognitive and motor side effects, should be investigated further. Examining EEG in other areas (e.g. temporal lobe, occipital lobe) may elucidate connections between seizure expression and the visuomotor side effects found in this study. Beyond the baseline and post-treatment markers obtained in this study, check-ins during treatment and three and six months following treatment termination would provide information regarding the time course of side effects. The feasibility of MST depends on whether it presents fewer, less

impairing, and less chronic side effects. Thus, neuropsychological outcomes should be assessed at regular intervals during and after treatment.

Overall, this study demonstrated the efficacy of MST in geriatric patients with severe depression, and identified patterns of ictal expression that may be indicative of therapeutic response. These results further support the feasibility and efficacy of MST as an alternative treatment to ECT.

Figures

Figure 1. Topographic map of ten frontal channels (circled) extracted

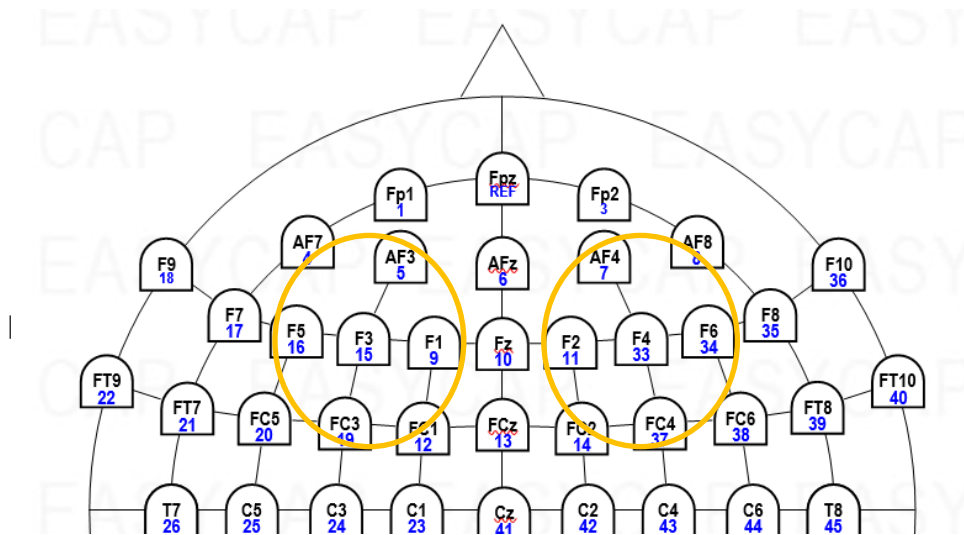


Figure 2. Power during ictal and post-ictal periods for start and end sessions. Error bars indicate standard error of the mean.



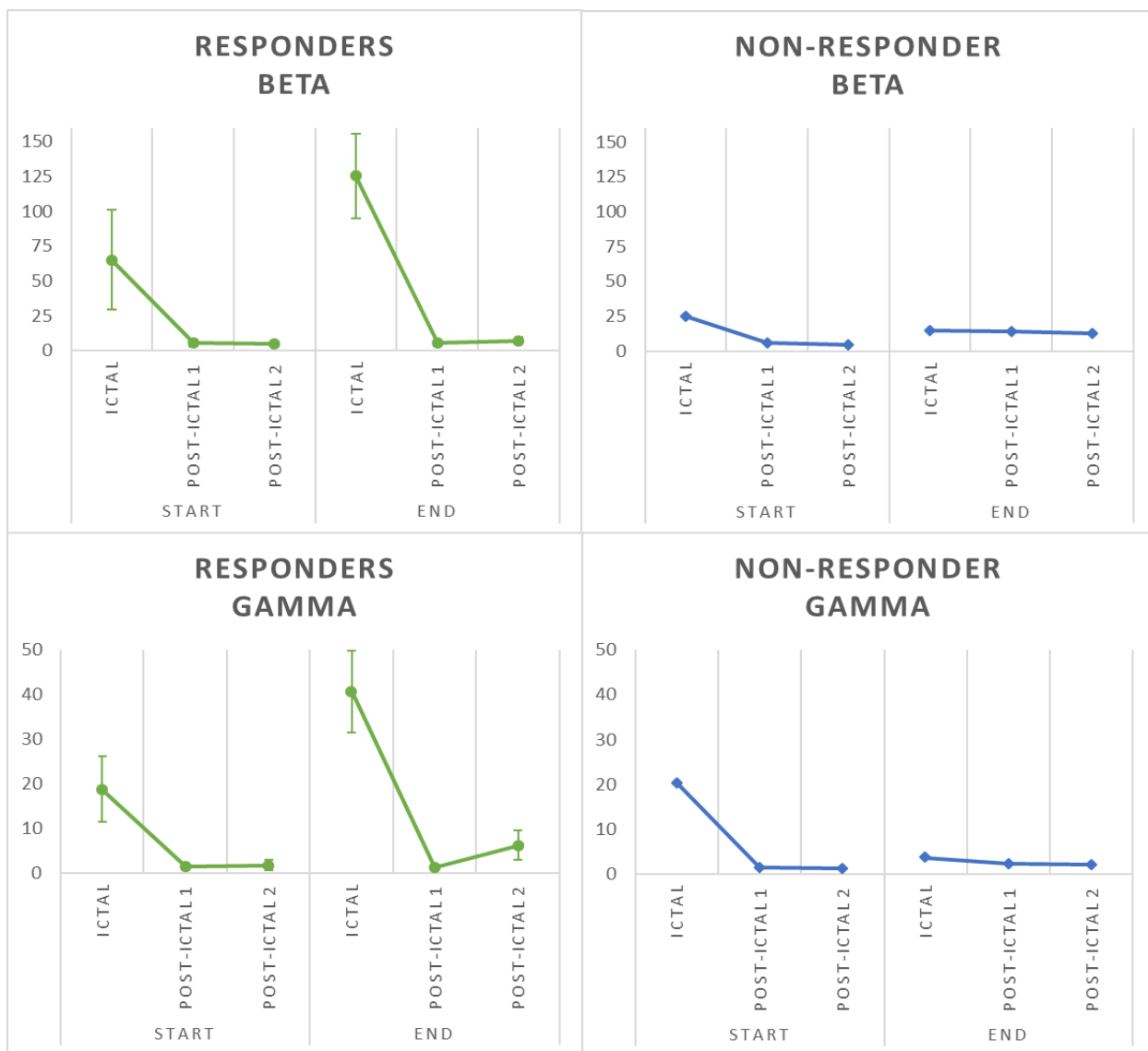


Figure 3. Relationship between change in Trails B/A ratio score and (a) change in ictal power or (b) change in post-ictal suppression in the gamma band.

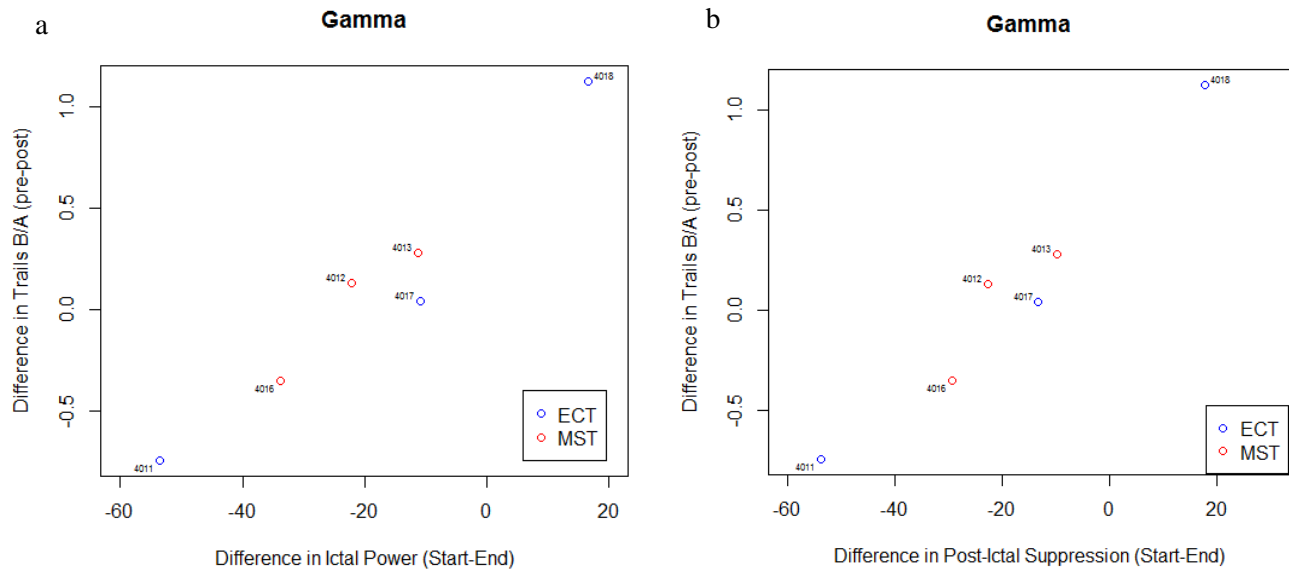


Figure 4. Relationship between change in COWAT score and (a) change in ictal power or (b) change in post-ictal suppression in the beta band.

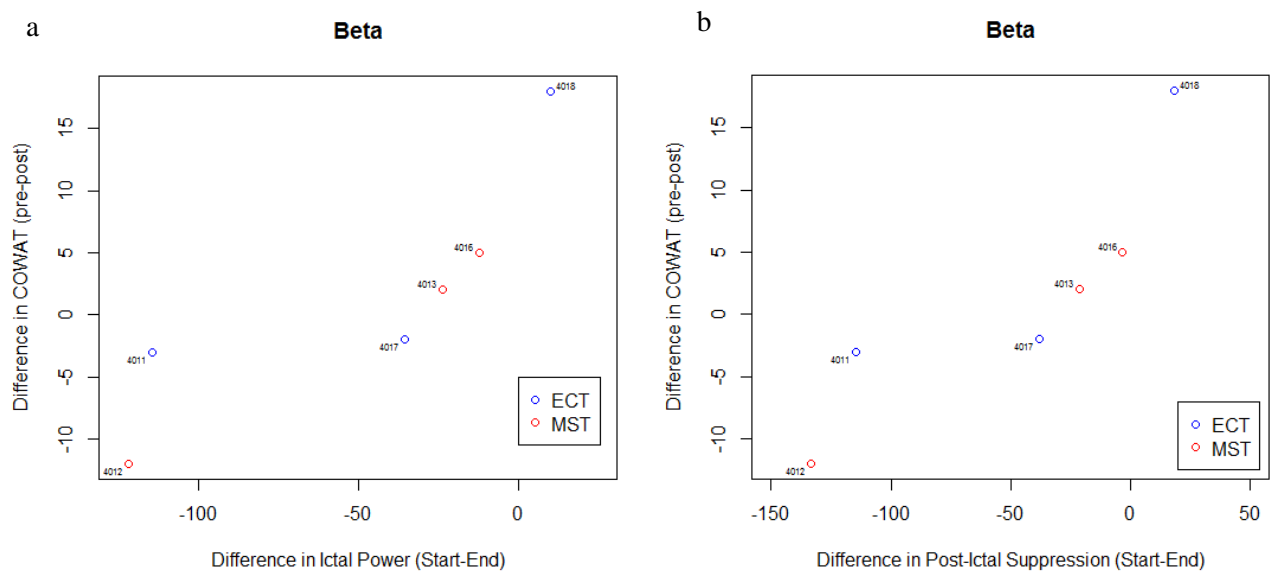


Figure 5. Relationship between change in COWAT score and (a) change in ictal power or (b) change in post-ictal suppression in the theta band.

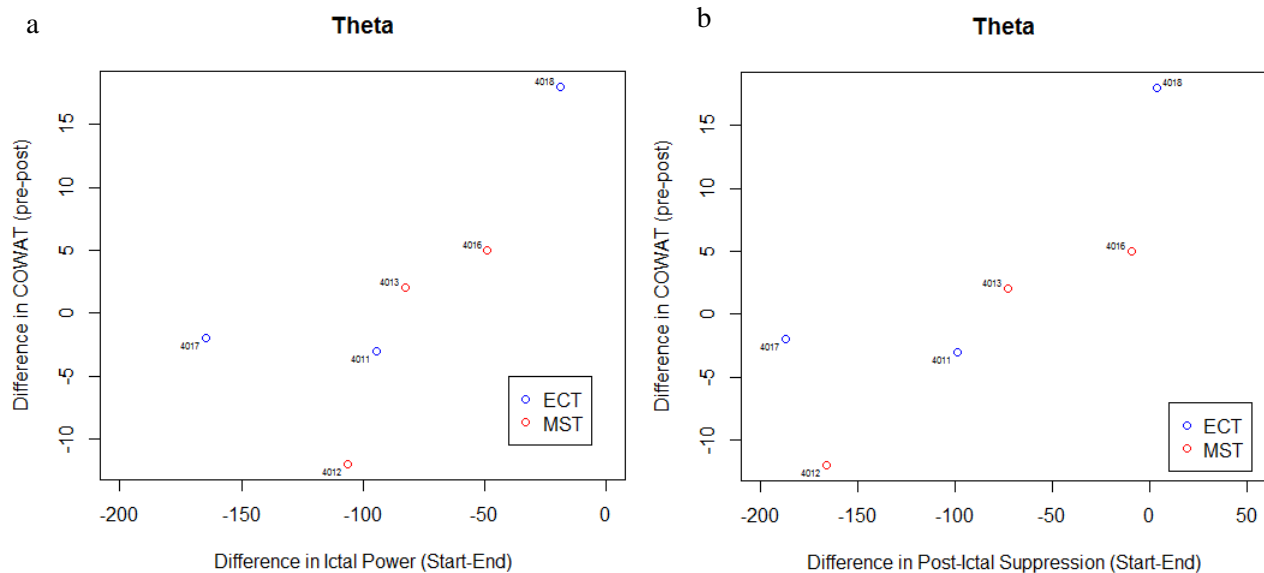
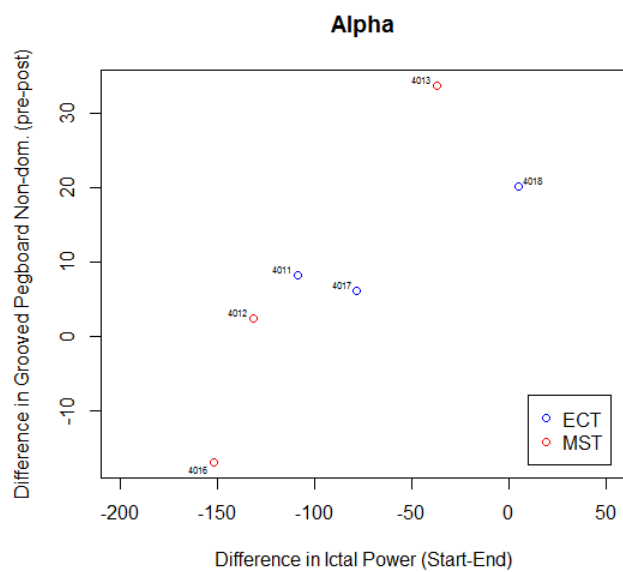


Figure 6. Relationship between change in Grooved Pegboard score and change in ictal power in the alpha band.



Tables

Table 1. Patient characteristics and treatment response

ID	Sex	Age	Treatment	# Sessions	Pre HRSD	Post HRSD	Status
4011	M	74	ECT	18	27	6	Responder
4012	F	62	MST	15	25	2	Responder
4013	F	74	MST	18	38	8	Responder
4016	F	63	MST	13	34	7	Responder
4017	F	57	ECT	16	26	7	Responder
4018	F	59	ECT	8	22	20	Non-responder

Table 2. Repeated-measures ANOVA to assess effects of treatment, session, period, and their interactions on average frontal power for five frequency bands (Greenhouse-Geisser corrected)

	Delta		Theta		Alpha		Beta		Gamma	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Treatment	0.06	0.82	0.44	0.56	0.26	0.65	0.39	0.58	0.71	0.46
Session	2.82	0.19	33.81	0.01*	12.59	0.04*	8.16	0.06+	8.47	0.06+
Period	3.92	0.14	2.35	0.22	4.97	0.11	5.55	0.10+	6.30	0.08
Treatment x Session	0.60	0.49	0.02	0.89	0.31	0.62	0.04	0.85	0.01	0.92
Treatment x Period	0.28	0.64	0.27	0.64	0.17	0.71	0.33	0.61	0.53	0.52
Session x Period	13.06	0.03*	14.12	0.03*	12.58	0.02*	4.64	0.12	8.23	0.05+
Treatment x Session x Period	5.60	0.10+	1.66	0.29	0.12	0.82	0.27	0.65	0.81	0.44

* $p < 0.05$, + $p \leq 0.10$

Table 3. Summary of hierarchical regression analysis for treatment and change in EEG (gamma) predicting change in Trails B/A ratio (N=6)

Variable	Model 1			Model 2a			Model 3a			Model 2b			Model 3b		
	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β
Treatment	-.12	.57	-.10	.05	.15	.04	.09	.36	.08	-.01	.15	-.01	.07	.37	.06
Change in EEG				.03	.003	.98**	.03	.004	.97*	.03	.003	.97**	.03	.004	.96*
Treatment x EEG							.002	.01	.05				.004	.02	.08
Adjusted R ²	-.24			.92			.88			.92			.88		
F for ΔR^2	.04			58.50**			.02			57.99**			.05		

+ p < .10, * p < .05, ** p < .01

Table 4. Summary of hierarchical regression analysis for treatment and change in EEG (beta) predicting change in COWAT score (N=6)

Variable	Model 1			Model 2a			Model 3a			Model 2b			Model 3b		
	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β
Treatment	-6.00	8.62	-.33	-5.10	4.72	-.28	-5.15	8.11	-.28	-4.93	4.32	-.27	-5.94	6.89	-.33
Change in EEG				.15	.05	.83*	.15	.08	.84	.14	.04	.85*	.15	.07	.92
Treatment x EEG							-.001	.11	-.005				-.02	.09	-.11
Adjusted R ²	-.11			.67			.50			.72			.59		
F for ΔR^2	.49			10.39*			<.001			13.01*			.05		

+ p < .10, * p < .05, ** p < .01

Table 5. Summary of hierarchical regression analysis for treatment and change in EEG (theta) predicting change in COWAT score (N=6)

Variable	Model 1			Model 2a			Model 3a			Model 2b			Model 3b		
	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β
Treatment	-6.00	8.62	-.33	-8.12	5.59	-.45	3.38	16.83	.19	-7.24	4.24	-.40	-6.85	8.26	-.38
Change in EEG				.16	.06	.79+	.14	.07	.70	.11	.03	.86*	.11	.05	.84
Treatment x EEG							.14	.19	.67				.004	.07	.03
Adjusted R ²	-.11			.54			.46			.73			.60		
F for ΔR^2	.49			6.73+			.54			13.65*			.004		

+ p < .10, * p < .05, ** p < .01

Table 6. Summary of hierarchical regression analysis for treatment and change in EEG (alpha) predicting change in Grooved Pegboard Non-dominant score (N=6)

Variable	Model 1			Model 2a			Model 3a			Model 2b		
	B	SE B	β	B	SE B	β	B	SE B	β	B	SE B	β
Treatment	-5.03	15.40	-.16	7.41	10.17	.24	31.37	10.54	1.00+	5.04	14.10	.16
Change in EEG				.27	.09	.93+	.12	.08	.41	.17	.10	.76
Treatment x EEG							.29	.11	1.19			
Adjusted R ²	-.22			.57			.86			.16		
F for ΔR^2	.11			8.21+			7.37			2.82		

+ p < .10, * p < .05, ** p < .01

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