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An electrophysiological biomarker that may predict treatment response to ECT

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Abstract

Objectives: Electroconvulsive therapy (ECT) is the most effective treatment for major depression (MDD), but also carries risk of cognitive side-effects. The ability to predict whether treatment will be effective prior to initiation of treatment could significantly improve quality of care, reduce suffering, and diminish costs. We sought to carry out a comprehensive and definitive study of the relationship between the background electroencephalography (EEG) and therapeutic response to ECT.

Methods: Twenty-one channel resting EEG was collected pre-ECT and 2–3 days following ECT course from two separate data sets, one to develop an EEG model of therapeutic response (N=30) and a second to test this model (N=40). A 3-way principal components analysis was applied and coherence and spectral amplitude across 6 frequency bands were examined. The primary outcome measure was the Montgomery Asberg Rating Scale (MADRS).

Results: Four patterns of amplitude and coherence along with baseline MADRS score accounted for 85% of the variance in post-treatment course MADRS score in Study 1 (R^2=0.85, F=11.7, p<0.0002) and 53% of the variance in MADRS score in Study 2 (R^2=0.53, F=5.5, p<0.003). Greater pre-ECT course anterior delta coherence accounted for the majority of variance in therapeutic response (Study1: R^2=0.44,p = 0.01; Study2: R^2=0.16,p = 0.008).

Conclusions: These results suggest a putative electrophysiological biomarker that can predict therapeutic response prior to a course of ECT. Greater baseline anterior delta coherence is significantly associated with a better subsequent therapeutic response and could be indicative of intact circuitry allowing for improved seizure propagation.

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Conflicts of Interest:

Dr. Krystal is a consultant for Ferring, Galderma, Jazz, Janssen, Takeda, Merck, Neurocrine, Otsuka, Pfizer, Lundbeck, Pernix, Idorsia, Adare, Harmony Biosciences. The other authors report no conflicts of interest.

Keywords

electroconvulsive therapy; major depressive disorder; biomarker; electroencephalography

INTRODUCTION:

Electroconvulsive therapy (ECT) is the most effective treatment for major depression (MDD) with short-course response rates reported up to 71%[1–3]. The ability to predict whether treatment will be effective prior to initiation of treatment or early in the treatment course could improve quality of care, reduce suffering, and diminish costs[4, 5]. While traditional biomarker development has focused on genetics, inflammatory and metabolic processes, or neurotransmitter components without large scale success, a new approach is to target dysfunctional activity in neural circuits to develop a neurophysiological biomarker of MDD[6, 7].

Neurophysiologic effects of ECT are manifest in the electroencephalogram (EEG) and have been the object of study since the 1940s[8–10]. Studies suggest that the EEG data recorded prior to and after the ECT treatment (eyes closed/waking/resting EEG activity referred to as the background EEG), could be used to calculate a biomarker for therapeutic response[11]. The majority of such studies point to the importance of low-frequency EEG activity in anterior regions[12, 13]. One study reported that there was greater anterior low-frequency EEG coherence (correlation specific to low-frequency EEG activity) between the cerebral hemispheres prior to the ECT in therapeutic responders[13] and another reported that a successful course of ECT induces a greater amplitude of anteriorly predominant low-frequency activity in the EEG after, compared with prior, to the treatment course[12]. EEG features, such as these, that provide an objective and quantifiable index of the biological process underlying depression and could be used as a predictor and correlate of therapeutic response would have a large impact on advancing our current treatment practices and in developing optimized and novel treatments.

Such efforts are similar, but distinct, from those in the 1990’s and early 2000’s that sought to find EEG determinates of ECT dosage during the ictal and post-ictal EEG. Those efforts revealed that specific features of the ictal EEG as well as post-ictal suppression, correlated with therapeutic response supporting the potential for spectral power and coherence as neural features that could potentially be used in biomarker development[11, 14–21]. Despite these findings, there are few studies since that have examined the background EEG as a treatment predictor of ECT.

In accordance with early background EEG findings, other studies have highlighted the importance of low frequency power spectra and coherence in predicting therapeutic response to serotonergic antidepressant medications, transcranial magnetic stimulation, and deep brain stimulation. Such measures have included theta and alpha pre-treatment power[22–31], alpha asymmetry[24, 32], theta cordance (a measure that combines absolute and relative theta power measures using a specific algorithm)[33–40], and the antidepressant treatment response (ATR, a measure of alpha and theta activity)[27, 31, 41–44]. The BRITE-MD trial, carried out in 67 adults with depression, the ATR measured at baseline and 1 week after treatment with

escitalopram was shown to predict remission at 13 weeks in a receiver operating characteristic analysis with a positive predictive value of 76%[44].

In the current study, we sought to examine the relationship between the background EEG and therapeutic response to ECT, independent of ECT type or stimulus dose. We employed a rigorous multivariate statistical technique, a 3-way principal components analysis, and studied both coherence and spectral amplitude. Furthermore, we utilized data from two separate data sets. We used one data set to develop an EEG model of therapeutic response (N=30) and then tested this model in a separate data set (N=40). Only features that were correlates of therapeutic response in both studies were retained.

MATERIALS AND METHODS:

STUDY 1.

EEG frequency spectral amplitude and coherence features were tested for their relationship to therapeutic outcome.

Subjects: Thirty Duke University Medical Center inpatients with major depression (DSMIII-R) who were right-handed, were at least 60 years old, and had not had ECT in 6 months were enrolled in this internal review-board approved study, with treatment and data collection done between 1986–1991. Efforts were made to keep subjects drug free prior to ECT for at least 5 days, with occasional utilization of small dosages of benzodiazepine or haloperidol as needed for extreme anxiety or clinically significant psychotic manifestations.

ECT Administration: All subjects received standard pulse (1–2 msec) right unilateral (UL) ECT (MECTA SR1 ECT device; MECTA Corp., Lake Oswego, OR, U.S.A.). ECT was administered three times a week. Routine pharmacological agents included IV bolus glycopyrrolate 0.2mg, followed by methohexital initially at 1 mg/kg and of succinylcholine at 1 mg/kg. Subjects were ventilated using positive pressure 100% oxygen by bag. Stimulus intensity was initiated at a fixed level of 168 mC for the first 22 subjects, with stimulus dosing for subsequent treatments utilizing titration followed by moderately suprathreshold levels thereafter to ensure EEG seizure durations of greater than or equal to 25 seconds as previously described[45]. Treatment continued until a plateau in therapeutic response was achieved (no additional improvement for two treatments in a row).

Therapeutic Outcome Measures: The Montgomery-Asberg Depression Rating Scale (MADRS)[46] was administered at baseline and 2–3 days following the ECT course by a single trained rater blinded to the EEG data. Response was assessed by comparing the post-course and pre-course MADRS score.

STUDY 2.

EEG correlates of therapeutic response in Study 1 were tested with Study 2 data in an attempt to replicate those findings.

Subjects: Forty Duke University Medical Center inpatients with major depression (DSMIII-R) who were right-handed and at least 30 years old were enrolled in this internal

review board approved study[47]. Nearly all subjects were off of psychotropic medication for mean of 6 days prior to the ECT course and had not had previous ECT in the prior 6 months. Nearly all subjects were psychotropic free throughout the ECT course, except that a very small fraction of these received small doses of chloral hydrate, oxazepam, or haloperidol, for control of severe insomnia, agitation or psychosis.

ECT Administration: Subjects received bitemporal (BL) brief pulse ECT. Pulse (0.5–1.0 msec) ECT was performed using the MECTA SR1 ECT device (MECTA Corp., Lake Oswego, OR, U.S.A.). Stimulus intensity was initiated utilizing titration followed by moderately suprathreshold levels thereafter to ensure EEG seizure durations of greater than or equal to 25 seconds as previously described[45]. Anesthetic medications were equivalent to those used in study 1.

Therapeutic Outcome: Therapeutic outcome measure was identical to that utilized in Study 1.

EEG Recording: For both Study 1 and Study 2 data, waking eyes-closed EEG data was recorded from 21 channels (including 2 eye-movement monitoring leads) of the International 10/20 System referenced to linked-ears with Ag/AgCl electrodes using a Nihon-Kohden EEG machine employing a 1–70 Hz bandpass filter and 60 Hz Notch filter (Nihon-Kohden Corporation, Irvine CA). The data was digitized at 102.4 Hz with 12 bits accuracy using the EEGSYS EEG acquisition and analysis system (Friends of Medical Science, Inc.). Data was collected over a 30-minute period prior to the first ECT treatment and 2–3 days after the treatment course. Data was collected in a dark, sound attenuated electrically shielded room. If patients became drowsy they were briefly stimulated by an auditory tapping sound. The data underwent manual artifact rejection by A.D.K. who is Board Certified in EEG.

Computer EEG Analysis: Fourier spectral amplitude and coherence were calculated from the fast Fourier transform (FFT) using the EEGSYS system (Friends of Medical Science, Inc.). FFTs were performed on non-overlapping 2 sec intervals tapered with a Hanning window. This employed the following frequency bands: δ = 1–4 Hz, θ = 4.2–8 Hz, α=8.2–13 Hz, β1=13.2–18 Hz, β2=18.2–30 Hz, and γ =>30 Hz. For the computation of coherence, the data was transformed to an anterior-posterior bipolar derivation. Coherence leads were: 8 Interhemispheric: 1) Fp1-F7 –> Fp2-F8, 2) Fp1-F3 –> Fp2-F4, 3) F7-T3–>F8-T4, 4) F3-C3–> F4-C4, 5) C3-P3–>C4-P4, 6)T3-T5–>T4-T6, 7) P3-O1–>P4-O2, 8)T5-O1–>T6-O2; and 24 Intrahemispheric: 1) T3-T5 – F3-C3, 2) T4-T6 – F4-C4, 3) T3-T5 – FP1-F7, 4) T4-T6 – Fp2-F8, 5) T3-T5 – P3-O1, 6) T4-T6 – P4-O2, 7) T3-T5 – C3-P3, 8) T4-T6 – C4-P4, 9) T3-T5 – Fp1-F3, 10) T4-T5 – Fp2-F4, 11) Fp1-F3 – C3-P3, 12) Fp2-F4 – C4-P4, 13) Fp1-F3 – F7-T3, 14) Fp2 F4 – F8-T4, 15) Fp1-F3 – P3-O1, 16) Fp2-F4 – P4-O2, 17) Fp1-F7 – F3-C3, 18) Fp2-F8 – F4-C4, 19) Fp1-F7 – C3-P3, 20) Fp2-F8 – C4-P4, 21) Fp1-F7 – P3-O1, 22) Fp2-F8 – P4-O2, 23) F3-C3 – P3-O1, 24) F4-C4 – P4-O2.

Statistical Analysis: All EEG data were transformed to the normal distribution prior to analysis[48]. Analyses were carried out using the SAS system (SAS Institute, Inc., Cary, NC, U.S.A) and utilized two-tailed tests of significance. On the first dataset, a 3-way principal components analysis (3PC) was carried out on EEG data from 3 conditions (pre-ECT, post-

ECT and post-pre ECT). Each principal component derived from summing the product of a series of constants with each of the z-transformed EEG variables (coherence or amplitude within each band and location). Z-transformation was performed by subtracting the mean and then dividing by the standard deviation of each EEG variable. The resulting principal components were uncorrelated linear transformations of the original variables with the relative size of the derived constants associated with each EEG variable reflecting the degree to which that variable contributed to the resulting principal component. Only the principal components where there was at least a trend ($p<0.10$) for them to have an individual contribution to explanation of variance in therapeutic response were retained in the model. Subsequently, the PCs were included with the difference in MADRS score (post-pre ECT course) in a multiple regression model developed to determine whether the EEG features identified through the principal component analysis correlated with therapeutic response. The EEG features identified through the 3PC model were tested on the second data set. The significant PCAs identified in dataset 1 were reconstructed using the EEG data from dataset 2 and entered into a regression model along change in MADRS score pre to post-ECT course. The univariate analysis was also repeated in dataset 2.

RESULTS:

Subject characteristics and response to ECT treatment for each study group are shown in Table 1. A set of 4 patterns of amplitude and coherence and the baseline depression score were found to be associated with therapeutic response in Study 1 and in Study 2 using 3PC. These patterns appear in Table 2 along with their direction of effect and the amount of variance they accounted for in therapeutic response. These 4 patterns along with baseline MADRS score accounted for 85% of the variance in post-treatment course MADRS score in Study 1 ($R^2=0.85$, $F=11.7$, $p<0.0002$) while these same patterns along with baseline MADRS score accounted for 53% of the variance in post treatment-course MADRS score in Study 2 ($R^2=0.53$, $F=5.5$, $p<0.003$).

It is notable that in both studies, greater pre-ECT course anterior inter and intrahemispheric delta EEG coherence was a predictor of subsequent therapeutic response and accounted for a substantial amount of the variance (Coherence 1, Table 2). In Study 1 greater anterior delta coherence accounted for 44% of the variance in therapeutic response. When post-ECT EEG was removed from the regression model to construct a model of response involving only pre-ECT coherence and pre-ECT course depression severity, greater anterior delta coherence accounted for 67% of the variance in therapeutic response. This effect was also present, though not as pronounced in Study 2. Pre-ECT anterior delta coherence accounted for 16% of the variance in therapeutic response. A model of response involving only pre-ECT coherence and depression severity revealed that anterior coherence within this band accounted for 33% of the variance in subsequent therapeutic response. These results suggest that greater anterior delta coherence in the background EEG is significantly associated with a better therapeutic response and may be an important biomarker of treatment prediction (Figure 1).

Several background EEG neural activity patterns in the post-course EEG also emerged from this analysis as being correlated with a positive therapeutic response. In both studies, a

smaller anterior delta coherence following the treatment course was associated with a better therapeutic response after controlling for baseline anterior delta coherence (Coherence 2, Table 2). In Study 1, this EEG variable accounted for 11% of the variance in therapeutic outcome, and in Study 2, 14% of the variance. It is notable that in a model including just pre and post treatment anterior delta coherence and pre-treatment therapeutic outcome accounted for 74% of the variance in therapeutic outcome in Study 1 and 40% of therapeutic outcome in Study 2. A smaller contribution was found for post-course pre-frontal theta and alpha coherence which accounted for 2% of the variance in therapeutic outcome in Study 1 and 6% in Study 2 (Coherence 3, Table 2).

The only spectral amplitude finding which emerged from the multivariate analysis was a relatively smaller effect (Power 4, Table 2). There was a trend for smaller prefrontal/frontal/ and anterior temporal gamma power to be seen following the treatment course in therapeutic responders. In Study 1 this EEG variable accounted for 5% of the variance in therapeutic response ($F=4.0$, $p<0.07$) and in Study 2 this variable accounted for 8% ($F=3.5$, $p<0.08$).

DISCUSSION:

While ECT has a high response rate, about 30% of patients will not adequately respond to ECT[1, 3]. There is utility in the exploration of safe and efficient methods to predict treatment response given the nature of the procedure and its side-effect profile (ex. 48% of patients report headache, 41% anterograde memory impairment, 37% confusion)[49]. This study identified a set of 4 EEG correlates of ECT response in the background pre- and post-course EEG that together with baseline depression score accounted for the majority of variation in the therapeutic response. The results were selected from among a set of promising indices and were identified independently in two different ECT research studies. The most predictive neural activity pattern identified was frontal delta coherence in the pre-course ECT. This potential biomarker accounted for 67% and 33% of the variance in the two research studies, with increased baseline coherence associated with better therapeutic outcome.

The identification of increased baseline anterior delta coherence as a biomarker of therapeutic response to ECT supports the research from Roemer and colleagues[13]. Our work extends their findings of interhemispheric coherence in the delta frequency band to that of intrahemispheric coherence and to pre-frontal sites. Our results also demonstrate the importance of coherence in higher frequency theta and alpha bands.

The underlying mechanism as to why low frequency coherence indicates improved response to ECT remains unknown. Decreased coherence at baseline points to a process that disconnects frontal and pre-frontal regions, which could reflect a decreased ability to synchronize and manifest a seizure that is widely and intensely expressed. We have strong evidence that seizure quality is associated with therapeutic response[18, 50, 51]. Loss of integrity of cortico-limbic and subcortical circuits are a leading candidate for inducing diminished coherence and preventing the response to ECT. White matter abnormalities would be expected to diminish the coupling between brain regions both from subcortical structures and within the cortex, particularly between the hemispheres. This relation could

explain why the effect was larger in Study 1 as patients in Study 2 were excluded if they had pre-existing cerebral disease. White matter hyperintensities in MRI scans have been observed to be more prevalent in depressed patients and associated with poor response to both pharmacotherapy and to ECT[52–55]. Patients with more severe subcortical gray matter hyperintensities were shown to have significantly less improvement after ECT[56]. Furthermore, a number of groups have reported that white matter lesions or damage lead to decreased EEG coherence[57–61]. Further research is needed into the relationship of vascular disease, white matter lesions, and low frequency coherence as a biomarker of treatment outcome.

While greater anterior delta coherence in the pre-course EEG predicted better therapeutic outcome, diminished anterior delta coherence predicted better outcome in the post-course EEG. This latter finding indicates that successful ECT appears to be associated with relatively diminished relationship between anterior brain regions. It is possible that successful treatment induces a relative disconnection of anterior regions. This effect might be mediated via a change in a sub-cortical structure which otherwise connects these regions, or more likely through enhanced inhibition in these areas, diminishing their activity in general. The latter hypothesis would be consistent with studies indicating that successful ECT decreases anterior cerebral metabolism and enhances cortical inhibition[62–64]. The tendency for smaller prefrontal/frontal and anterior temporal gamma frequency activity to be seen following the treatment course in therapeutic responders is also consistent with enhanced inhibition following ECT in responders.

Delta oscillations in EEG have been implicated in a range of normal human functions including slow wave sleep, memory processing, motivation and cognitive processing[65]. An increase in resting delta activity is also observed in pathological states associated with developmental disorders or brain damage[66, 67], as well as in neuropsychiatric disorders including depression[68–72]. Pizzagalli and colleagues have shown that patients with melancholic depression exhibited increased delta activity in the subgenual prefrontal cortex which decreased post-treatment with nortriptyline[73]. This finding was supported by others that demonstrated a positive correlation between delta activity in the cingulate cortex and anhedonia scores[74], and increases in delta power and coherence through this same network when subjects were given negative feedback during an anxiety task[75]. It may be that subjects with altered activity within this low frequency band may reflect a specific subtype of major depression characterized by anhedonia and that this subset of patients may respond best to ECT.

Major depression is associated with functional and structural dysfunction within cortico-striatal and limbic circuits[76–81]. One such circuit is the default mode network (DMN), a large resting state network comprised of cingulate and frontal regions such as the dorsomedial prefrontal cortex among others[76]. Patients with depression exhibit hyperactivation of the DMN during task-specific activity suggesting that they are unable to flexibly switch between cognitive/attention networks and resting-state networks[82, 83]. Increased connectivity both within the DMN network itself and between the regions of this network and other MDD regions is also observed[84, 85]. It is tempting to speculate that our observation of increased frontal delta coherence may reflect altered activity within the

DMN. In a study designed to examine the resting-state spectral distribution in EEG field powers of the DMN, large pre-frontal delta and smaller fronto-central theta was observed, consistent with this hypothesis[86].

The development of physiological biomarkers of treatment response in major depression would be a significant advance in the field of psychiatry. For patients and providers considering ECT, a biomarker of treatment response that predicted response prior to first treatment could reduce unnecessary cost, risk, and side-effects for the patient and reduce suffering by allowing the patient and provider to more quickly select the treatment with the highest probability for success. Across the field as a whole, a biomarker is critical for the development of novel therapies, allowing for the ability to back translate findings to animal models to advance our understanding of disease pathophysiology, and for development of an analytical personalized approach to mental health. Studies investigating EEG as a putative biomarker of treatment response for antidepressants have focused predominantly on three neural activity patterns. First is alpha asymmetry, with studies showing decreased frontal alpha power (8–12 Hz) in the right vs. left hemisphere in non-responders[32, 87], although the temporal stability of these findings limits their translation into a clinical setting[88–91]. Second are theta rhythms (4–8 Hz), which have been implicated in memory and cognition[92–94]. Studies have focused on theta cordance as a putative biomarker, a composite measure that relates relative power within the theta band to absolute power within this band[33]. Decreased frontal theta cordance after 1 week of treatment is observed in MDD responders to antidepressants,[29, 35, 37, 39] DBS[36] and rTMS[34, 35]. The third measure is the antidepressant treatment response (ATR) index, which combines EEG frontal power features in the theta and alpha bands from a pre-treatment EEG and a second EEG one week after treatment[27, 31, 42–44, 95, 96]. Both the ATR and theta cordance typically rely on neural activity obtained at baseline and after 1 week of treatment. Ideally, a biomarker would predict outcome prior to any treatment initiation, perhaps particularly in the case of ECT which has higher costs and potential side effects than pharmacological treatments. A study by Stubbeman and colleagues found that central theta cordance measured using only the pre-course ECT was highly correlated with post-course ECT response[97]. The authors suggest that differential activity between responders and non-responders in the cingulate cortex may underlie the difference in therapeutic response to ECT. A meta-analysis of 19 neuroimaging studies support their hypothesis, showing that pre-treatment rostral anterior cingulate (rACC) activity was a reliable biomarker of treatment response across several treatment modalities[98]. It should be noted, that the rACC is also part of the DMN, and theta cordance, together with frontal delta coherence, could both represent EEG biomarkers of dysfunction along nodes within this same network. There are several limitations of our investigation. First, the subjects underwent differing ECT modalities in the two studies, specifically standard pulseRUL in Study 1 and brief pulse BL in Study 2. While the ECT type may influence the post-ECT EEG it should not alter the pre-course ECT biomarkers observed in our findings. We cannot state that our findings are generalizable to all ECT treatments including ultra-brief pulse ECT, or all antidepressant treatments in general. If high delta coherence is a reflection of altered DMN connectivity, one might expect this biomarker to be independent of treatment type. Alternatively, if it is a reflection of local white matter integrity, it may have implications that extend only to how well a seizure is propagated and

may possibly be influenced by ECT stimulation parameters. The fact that the model was able to predict response for both UL and BL ECT provides support for its utility across different ECT settings. Second, subjects in Study 1 were older which may have had an effect on the slow wave activity and connectivity as older patients show neurophysiological EEG changes independent of white matter disease[99, 100]. Third, we limited the scope of this paper to an exploration of power and coherence variables that are correlated with depression outcome in a continuous model. The findings lend support for additional analyses in future studies. While coherence is used to infer connectivity or synchrony between two brain areas, it can be affected by volume conduction. Future work could explore the Imaginary Part of Coherency (ICOH) in addition to the 'real' coherence values[101]. Furthermore, future work could explore how well frontal delta coherence could be used as a screening tool to classify future responders and non-responders to ECT through a binary classifier and sensitivity analysis. Finally, a biomarker of adverse events of ECT such as cognitive side-effects could be explored. Overall, our results suggest EEG may be used to identify a consistent neurophysiological biomarker that is stable across studies and warrants further investigation with larger samples and other types of ECT therapies.

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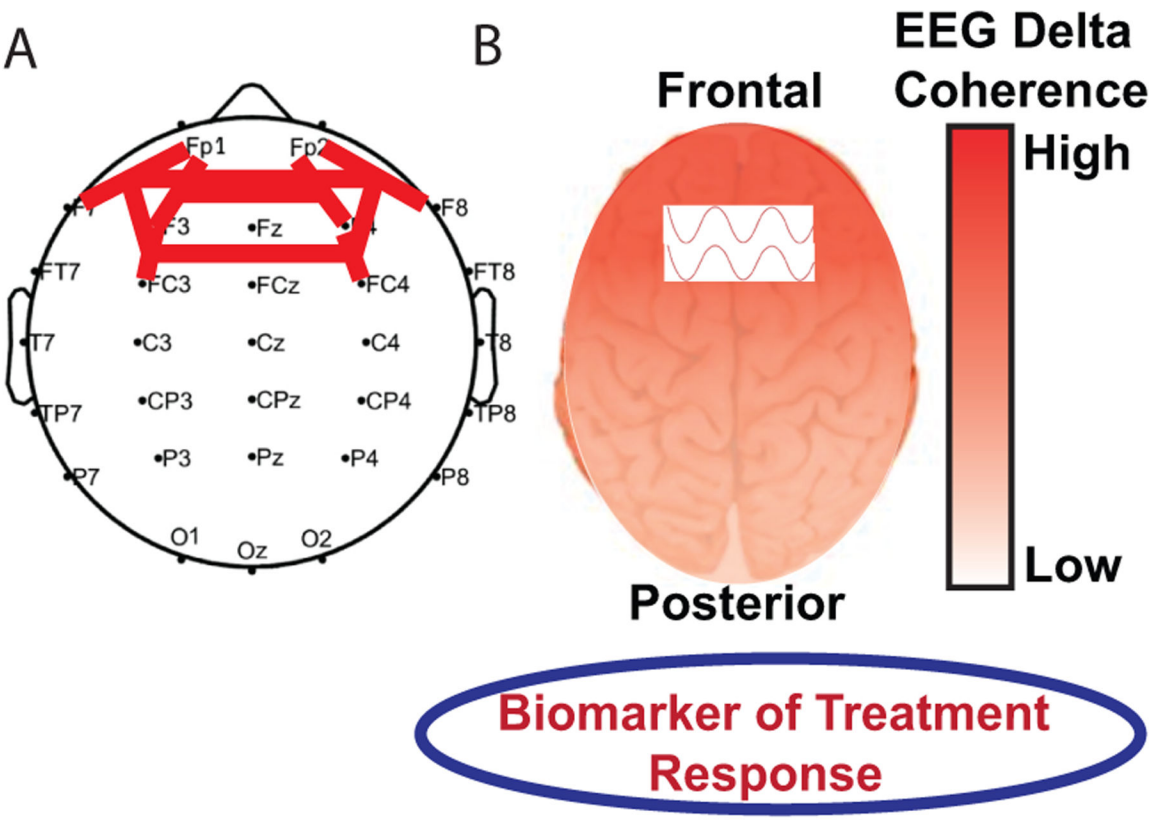

Figure 1.

Biomarker of Treatment Response. A. Interhemispheric and intrahemispheric coherence leads where pre-ECT delta coherence was a predictor of subsequent therapeutic response. B. Schematic showing greater anterior delta coherence in the background EEG is associated with a better subsequent therapeutic response to ECT and may represent an important biomarker of treatment prediction.

Table 1.

Subjects and Outcomes

Characteristic	Study 1 (n = 30)	Study 2 (n = 38)
Mean age (SD)	75.5 (20.5)	54.4 (17.0)
Mean baseline MADRS score (SD)	34.0 (10.0)	34.7 (6.7)
Mean MADRS difference score (post ECT - baseline) (SD)	24.3 (11.3)	17.9 (9.1)
50% reduction in MADRS from baseline (n)	25	21

Patient characteristics, depression rating scores, and response rate to ECT for each study group. SD = standard deviation, n = number

Table 2.

Neural Activity Patterns Associated with Therapeutic Response

Measure	Study 1			Study 2		
	R^2	M	p-value	R^2	M	p-value
1. Baseline Pre-Frontal and Fronto-Central Delta Coherence	0.44	−6.7	0.01	0.16	−5.4	0.008
2. Post-course Pre-Frontal and Fronto-Central Delta Coherence	0.11	9.4	0.015	0.14	3.4	0.006
3. Post-course Pre-Frontal Theta and Alpha Coherence	0.02	−5.9	0.06	0.06	−1.2	0.09
4. Post-course Pre-Frontal and Anterior Temporal Gamma Power	0.05	5.6	0.07	0.08	1.3	0.08
Baseline Depression Rating	0.24	0.57	0.002	0.09	0.3	0.04

Four neural activity patterns and baseline depression rating score accounted for the majority of variance in post-ECT depression rating scores. Each pattern with its associated R^2, magnitude of response (M) and p-value for the regression model is shown for Study 1 and the validation dataset (Study 2).