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RESEARCH ARTICLE

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Association between increased theta cordance and early response to ECT in late-life depression

Michael J. Ward[1] | Helmet T. Karim[2] | Zachary F. Jessen[3] | Avniel Singh Ghuman[1,2,4,5] | R. Mark Richardson[1,4] | Charles F. Reynolds III[2] | Jordan F. Karp[2]

[1] Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA

[2] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

[3] Medical Scientist Training Program, Northwestern University, Chicago, IL

[4] Center for the Neural Basis of Cognition, Carnegie Mellon University and University of Pittsburgh, Pittsburgh, PA

[5] Program in Neural Computation, Center for the Neural Basis of Cognition, Carnegie Mellon University and University of Pittsburgh, Pittsburgh, PA

Correspondence
Jordan F. Karp, MD, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.
Email: karpjf@upmc.edu

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Objectives: More than half of patients with major depression who do not respond to initial antidepressants become treatment resistant (TRD), and while electroconvulsive therapy (ECT) is effective, it involves anesthesia and other medical risks that are of concern in geriatric patients. Past studies have suggested that theta cordance (TC), a correlate of cerebral metabolism measured by electroencephalography, could guide treatment decisions related to patient selection and engagement of the therapeutic target.

Methods/Design: Eight patients with late-life treatment resistant depression (LL-TRD) underwent magnetoencephalography (MEG) at baseline and following seven sessions of ECT. We tested whether the mean and regional frontal cortex TC were able to differentiate early responders from nonresponders.

Results: Five patients whose depression severity decreased by >30% after seven sessions were considered early responders. We found no baseline differences in mean frontal TC between early responders compared with nonresponders, but early responders exhibited a significant increase in TC following ECT. Further, we found that compared with nonresponders, early responders exhibited a greater change in TC specifically within the right prefrontal cortex.

Conclusions: These results support the hypothesis that increases in frontal TC are associated with antidepressant response. We expand on previous findings by showing that this change is specific to the right prefrontal cortex. Validation of this neural marker could contribute to improved ECT outcomes, by informing early clinical decisions about the acute efficacy of this treatment.

KEYWORDS

depression, ECT, late life, neural marker, theta cordance

1 | INTRODUCTION

Depression is the second most prevalent psychiatric disorder in older adults, and one-third of late-life depressed patients are treatment resistant (LL-TRD), having failed to respond to multiple treatments.[1] Electroconvulsive therapy (ECT) is an effective option for TRD, with 70% initial response rates.[2] However, the risks of ECT (especially anesthesia) in late life are elevated; thus, identifying pretreatment response predictors is imperative.

LL-TRD has been linked to cerebrovascular disease,[3] and regional cerebral blood flow (rCBF) is associated with cerebral metabolic rate.[4] Thus, these markers of neural health may guide treatment

Mr Ward and Dr Karim are considered cofirst authors for this paper.

selection and prognosis. Patients with LL-TRD (compared with age-matched controls) have severe perfusion deficits in the prefrontal cortex,[5] and hypoperfusion in the anterior cingulate cortex is associated with LL-TRD.[6]

Theta cordance (TC) is a well-documented quantitative electroencephalography (QEEG) measure of cerebral energy consumption.[7,8] Prefrontal cortex TC has been associated with antidepressant response[9] and has a stronger association with perfusion than standard QEEG measures.[10] Additionally, TC is not influenced by age and health status,[11] strengthening its possible utility as a biomarker for response in LL-TRD.

One study reported that treatment refractory patients with higher pretreatment central TC were more likely to respond to ECT.[12] However, findings of metabolic studies using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have been mixed, with some suggesting low baseline rCBF that increases following treatment[13-15] and others showing decreased rCBF and regional glucose metabolism following treatment.[16-18] Among these studies, one found that there was an increase just 2 weeks after ECT treatment,[13] and another found a decrease at both 50 minutes and 1 week[16] after treatment. Another study described increased frontal theta-band activity after successful treatment for depression with ECT,[19] but TC was not examined. Together, these studies do not provide a clear description of the neural or metabolic changes that occur following ECT.

In this proof-of-concept pilot project, we hypothesized that an early change in prefrontal cortex TC is implicated in depression response to electrical stimulation following treatment with ECT. We sought to (*a*) identify baseline TC differences associated with response and (*b*) identify changes following ECT associated with response. Unlike other studies of TC in depression, which relied on electroencephalography (EEG), we used magnetoencephalography (MEG) to precisely localize, for the first time, the spatial origin of TC changes within the frontal cortex.

Key points

- Compared to nonresponders, early responders to ECT exhibited a greater change in theta-cordance (a measure of cerebral energy consumption) specifically within the right prefrontal cortex.
- These changes were observed after seven sessions of ECT it is possible that these markers change prior to clinical response and may help guide the early phase of interventions.
- Future studies should investigate if these changes occur even earlier (e.g., after a single ECT session) and predict future response.

2 | METHODS

We recruited eight patients who had major depressive disorder (MDD) or bipolar disorder (diagnosed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV) who were being treated with ECT. All patients scored ≥22 on the Montreal Cognitive Assessment[20] and were at least 50 years old. Exclusion criteria included major neurocognitive disorder, history of stroke, or diagnosis of psychotic-spectrum illness. Patients whose 17-item Hamilton Depression Rating Scale (HDRS-17)[21] decreased by >30% after seven sessions were considered early responders. These criteria for early response were selected because (*a*) patients were very ill, and we did not expect full criteria for response (>50% improvement) after only seven sessions (administered two to three times/week), and (*b*) improvement by 27% after 2 weeks of pharmacotherapy is predictive of remission.[22] Pharmacotherapy remained stable throughout the course of ECT treatment. This study was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent prior to participating.

Spontaneous, resting-state MEG activity was recorded before and after treatment using a whole-head 306-channel Elekta Neuromag Vectorview system (Helsinki, Finland). Patients were instructed to fixate their gaze on a crosshair for 10 minutes sitting upright. Empty-room MEG data were recorded to assess noise covariance. Signals recorded at 1000 Hz were bandpass filtered (1-45 Hz). Magnetometer data were excluded, leaving 204 gradiometer channels. Data were divided into 2-second segments and visually inspected for bad segments. Ocular and cardiac artifacts were removed using Infomax independent components analysis[23] after principal components analysis dimension reduction to 120 components.

Structural T1-weighted magnetic resonance (MR) images were obtained (Siemens 3 Tesla scanner). Both research and clinical MR scans were used. A cortical surface model using FreeSurfer was computed, and coregistration was performed between structural magnetic resonance imaging (MRI) and MEG fiducial markers. Preprocessed MEG data were projected onto the cortical space using the minimum norm estimator (MNE package).[24]

Frequency power at each cortical point was computed using discrete fast Fourier transform of each 2-second segment. Relative theta power was calculated by dividing absolute theta power (summing power from 3.5 to 7.5 Hz) by total power (summing power from 0.5 to 20.0 Hz). Absolute and relative theta power was normalized by calculating the *Z*-statistic across cortical points. TC was calculated as the sum of the normalized absolute and relative theta powers and averaged across segments. Individual data were morphed onto a reference brain for group analysis using MNE toolbox.

We performed two sample *t*-tests or chi-squared tests to examine differences in clinical and demographic features in the response group. A two-way mixed ANOVA (group with two independent factors and time with two repeated factors) was then implemented to test for group by time interactions for TC. We

TABLE 1 Demographic and clinical features between groups

	Nonresponders (N = 3)		Responders (N = 5)			
	Mean	SD	Mean	SD	Wilcoxon with Chi-square	*P* Value
Age	66	5	61	7	19.0	.294
Sex (F)	1		5		4.4	.035*
Diagnosis (MDD; BPD)	3; 0		2; 3		2.9	.09
Baseline HDRS	24	3	26	5	11.5	.546
Follow-up HDRS	18	8	16	6	22.0	.881
Number of antidepressants (1; 2; 3)	2; 1; 0		1; 3; 1		9.5	.191
Number on antipsychotics	1		3		11.5	.495
Number on stimulants	0		1		12.0	.439
Number of benzodiazepines (1; 2)	1; 1		3; 0		20.5	.514
Number of sedatives (0; 2)	2; 1		5; 0		20.0	.197

Abbreviations: BPD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.

*$P < .05$.

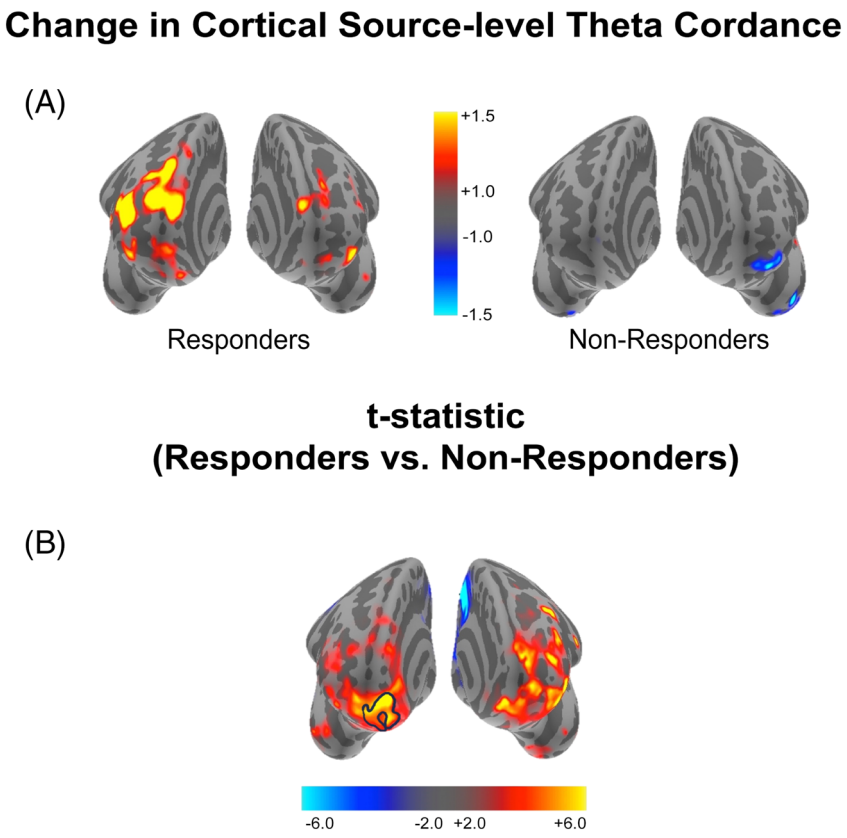

FIGURE 1 A, Theta cordance averaged across the entire frontal cortex in five responders (left) and three nonresponders (right). B, Cluster-based permutation test of responders and nonresponders. The outlined area in right medial prefrontal cortex denotes a significant cluster ($P = .016$). Note: gyri are denoted by darker gray while sulci are lighter gray

subsequently performed sensitivity analyses to test that the effects were independent of baseline depression severity, diagnosis, and age. To evaluate if particular areas of frontal cortex showed significant group differences in TC change, we performed permutation testing to assess differences between groups. A clusterwise multiple comparisons correction was conducted with a cluster-forming threshold of $P < .001$. We used the cluster-based permutation test described by Maris and Oostenveld to determine the regions that showed this change.[25]

3 | RESULTS

Five patients had >30% decrease in depression severity after seven ECT sessions (early responders). We found significant group differences by sex (early responders were females), but no differences in other demographic or clinical features (Table 1).

The cortical distribution of TC is presented in Figure 1, and the mean frontal TC is shown in Figure 2. To measure whole-brain TC, we averaged over the entire frontal cortex using the Desikan-Killiany

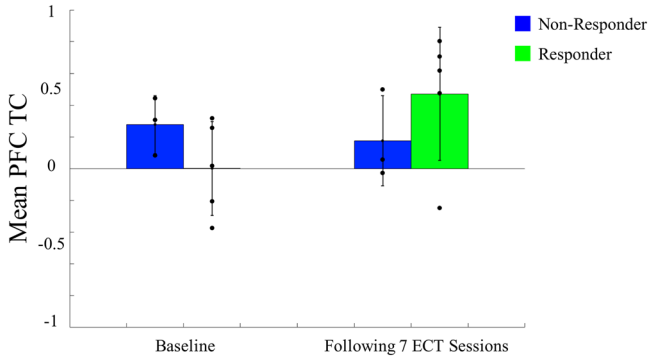

FIGURE 2 Plot of mean prefrontal cortex (PFC) theta cordance (TC) at baseline and following seven electroconvulsive therapy (ECT) sessions in nonresponders (blue, N = 2) and responders (green, N = 5). Individuals' responses for each participant are also shown (black dots)

TABLE 2 Theta cordance (TC) at baseline and follow-up in each of the responders and nonresponders to ECT

	Baseline	Follow-up	Change
Nonresponders	0.082	−0.029	−0.11
	0.444	0.5	0.056
	0.307	0.057	−0.249
Mean (SD)	0.277 (0.183)	0.176 (0.284)	−0.101 (0.153)
Responders	−0.374	−0.247	0.127
	0.257	0.618	0.362
	0.318	0.477	0.159
	0.017	0.803	0.786
	−0.205	0.705	0.91
Mean (SD)	0.003 (0.295)	0.471 (0.419)	0.469 (0.361)

Atlas (Table 2). We found that early responders demonstrated a greater increase in TC compared with nonresponders [interaction, $F_{1,6}$ = 6.5, P = .044] (Figure 2). This shift remained significant after sensitivity analysis for baseline depression severity, diagnosis, and age. We could not adjust for sex, as it was collinear with response. Additionally, only the change in TC was significant, and we found no significant differences in frontal TC between groups at baseline [t_6 = 1.4, P = .203] or after seven sessions [t_6 = −1.1, P = .328]. Because of the small sample sizes, we also report the nonparametric Wilcoxon signed rank test comparing baseline with after seven sessions in early responders (Z = −2.0, P < .043) and nonresponders (Z = −1.1, P = .285).

Early responders (compared with nonresponders) showed a greater increase in TC in one cluster in the right inferior-medial prefrontal cortex (peak t-stat at x = 9, y = 52, z = −3, Brodmann area 10 and 1000 repetitions, permutation P = .016, multiple comparisons corrected).

4 | DISCUSSION

We found an interaction between group and time, where after seven ECT sessions, there was a more positive TC change in early responders compared with nonresponders, but no differences in TC between groups at baseline or following the seven treatment sessions. This increase occurred in the right prefrontal cortex, which we speculate may be due to the laterality of the applied ECT stimulation. Our results replicate one past finding on theta activity[19] and support the subset of the literature that shows an increase in metabolism following ECT. We did not replicate another finding that associated higher pretreatment central cordance with greater response in ECT; however, those investigators did not examine change.[12]

Since TC is a measure of cerebral energy consumption,[7,8] we relate our results to findings of cerebral perfusion/metabolism. Most past studies have focused on cerebral perfusion and metabolism following ECT and have found mixed results. One set of studies described a significant decrease in rCBF in anterior cingulate 45 minutes after an ECT session[17]; rCBF globally 2 to 10 days following ECT, particularly in anterior, cerebral regions[16]; and regional glucose metabolism in frontolimbic areas approximately 5 days after ECT.[18] In contrast, another set of studies found a significant increase in rCBF in frontal areas and the anterior cingulate 5 to 8 days after ECT[14]; rCBF in the medial frontal region 1 month after ECT[15]; and increased rCBF in the anterior cingulate, orbitofrontal cortex, right insula, and right middle frontal gyrus at 2 and 12 weeks after ECT.[13]

The discrepancy in PET/SPECT neuroimaging data may be related to the utilization of a reference region, which is assumed to be unaffected in a particular process, often the cerebellum. One study, however, found that conditional use of the cerebellum as the reference affected the directionality of rCBF in other regions.[26]

We were able to show differences in TC change in a particular region of the right prefrontal cortex using MEG. As ECT stimulation was targeted near right prefrontal cortex for each patient, it is possible that this region is the central locus of the actual neural response and other surrounding regions may be recruited to a lower degree. Because of the greater temporal resolution of MEG than either MRI or EEG, we were able to show changes in a specific region in the brain. However, given the barriers of high cost and limited accessibility to MEG devices, it is important that these results be replicated in tandem with more cost-effective and accessible technologies like MRI and EEG. There are several studies in which EEG patterns predict antidepressant response and support the future use of this more scalable measure of brain electrophysiology as a predictor of response to ECT.

While we did not show baseline differences, responders showed (on-average) a lower baseline TC. Sample size may influence this effect, since there were only three nonresponders. Identifying individuals that may benefit from ECT prior to treatment is important to avoid costly and invasive treatments. Past studies have been mixed and have described both greater[12,16-18] and lower[13-15] pretreatment TC as a predictor of response. A larger study on the effects of ECT using MRI cerebral blood flow measurements combined with MEG data is needed to clarify these discrepancies and establish whether pretreatment TC can predict future response to ECT.

Sample size is a major limitation of this pilot study, which may make the observations unstable. However, given the paucity of actionable neural biomarkers to guide treatment with ECT, especially

in older adults who are at elevated risk of adverse effects, this topic warrants further investigation. Other limitations include lack of a control group and no follow-up beyond the seven sessions of ECT to evaluate the evolution and stability of this very conservative definition of response. All of the participants received right unilateral stimulation, so the observed response laterality may be related to treatment laterality. Depression response is traditionally defined as 50% improvement; however, we selected 30% improvement a priori to the analysis because of the severity of illness in our patients, as this may suggest they are on track to a more robust recovery. Future studies should follow patients longitudinally and more conservatively define response and remission. Finally, unlike EEG, MEG detects tangential but not radial components of a current source and thus has greater sensitivity to sulci. MEG also has a significantly greater spatial and temporal resolution. Both of these could contribute to differences between our results and those in the published brain electrophysiology literature. Future studies would ideally combine simultaneous recording from EEG and MEG. MEG is significantly more expensive and less accessible; however, EEG would be a relatively cost-efficient method to measure these changes. Finally, there were differences in sex and diagnoses in the responders (5 female, 2 MDD) and nonresponders (1 female, 3 MDD) groups, which may influence such a small sample.

5 | CONCLUSION

In summary, this study is the first to measure TC response to ECT using MEG and highlights the putative role of the prefrontal cortex in successful depression treatment with ECT. These results have the potential to inform future, more-localized studies using ECT or other stimulation treatments. MEG is not influenced by reference regions, does not expose patients to ionizing radiation (unlike PET or SPECT), and has greater spatial resolution than EEG. If validated, this biomarker may improve pretreatment and early treatment decisions regarding whether ECT will help a particular patient and may also be used to track engagement of targeted brain regions.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ORCID

Helmet T. Karim https://orcid.org/0000-0002-9286-0694

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