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Archival Report

Variations in Hippocampal White Matter Diffusivity Differentiate Response to Electroconvulsive Therapy in Major Depression

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ABSTRACT

BACKGROUND: Electroconvulsive therapy (ECT) is an effective treatment for severe depression and is shown to increase hippocampal volume and modulate hippocampal functional connectivity. Whether variations in hippocampal structural connectivity occur with ECT and relate to clinical response is unknown.

METHODS: Patients with major depression (n = 36, 20 women, age 41.49 ± 13.57 years) underwent diffusion magnetic resonance imaging at baseline and after ECT. Control subjects (n = 32, 17 women, age 39.34 ± 12.27 years) underwent scanning twice. Functionally defined seeds in the left and right anterior hippocampus and probabilistic tractography were used to extract tract volume and diffusion metrics (fractional anisotropy and axial, radial, and mean diffusivity). Statistical analyses determined effects of ECT and time-by-response group interactions (>50% change in symptoms before and after ECT defined response). Differences between baseline measures across diagnostic groups and in association with treatment outcome were also examined.

RESULTS: Significant effects of ECT (all $p < .01$) and time-by-response group interactions (all $p < .04$) were observed for axial, radial, and mean diffusivity for right, but not left, hippocampal pathways. Follow-up analyses showed that ECT-related changes occurred in responders only (all $p < .01$) as well as in relation to change in mood examined continuously (all $p < .004$). Baseline measures did not relate to symptom change or differ between patients and control subjects. All measures remained stable across time in control subjects. No significant effects were observed for fractional anisotropy and volume.

CONCLUSIONS: Structural connectivity of hippocampal neural circuits changed with ECT and distinguished treatment responders. The findings suggested neurotrophic, glial, or inflammatory response mechanisms affecting axonal integrity.

Keywords: Antidepressant, Brain stimulation, Diffusion MRI, ECT, Tractography, White matter

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Depression is a major burden to global health and the number one cause of years lost to disability (1). Though it is treatable, only half of symptomatic individuals are anticipated to respond to initial antidepressant therapies, whereas a third are expected to remain unresponsive to multiple treatments (2,3). To foster more successful outcomes in individual patients, targeting biological markers of clinical response is a primary goal of depression treatment research. Electroconvulsive therapy (ECT) is the most effective prescribed treatment for severe and intractable depression in patients with poor response to standard pharmacotherapies (4). Furthermore, clinical response occurs quickly with ECT, and remission can occur in as little as 2 to 4 weeks (5,6), which is more favorable than response times for standard antidepressants (7). However, whether particular neurobiological characteristics influence therapeutic outcome to ECT or other depression treatments is less clear.

A large body of literature supports that the heterogeneous presentation of depression encompasses abnormalities in neural structure (8–10) and dysregulations in structural (11) and functional (12–18) connectivity. The hippocampus is particularly implicated—in the largest depression meta-analysis of subcortical structure conducted to date, disease-related reductions in hippocampal volume showed the greatest effect sizes (19). In line with prior studies showing that disease duration and severity negatively impact volume (20,21), meta-analytic results also indicate more pronounced hippocampal volume reductions in recurrent depression (19). Abnormalities in hippocampal functional circuitry, which include the default mode and affective networks, are similarly observed (22,23) and are reported as modulated by treatment (24).

Prospective neuroimaging studies have shown normalization of neural structure and function with ECT (25–28). Reports of volume increases of the hippocampus before and after ECT

are consistently replicated (29–31). Increases in tissue volume or thickness are also reported in connected limbic, neostriatal, and cortical association regions (25,26) and in resting-state networks linking these regions (25,27,28,32–35). Relatively few investigations have addressed whether white matter connectivity changes in relation to ECT. However, in small samples and using whole-brain, region-of-interest, or graph theory network analysis approaches, data suggest that ECT modulates frontolimbic and temporolimbic white matter pathways (36–38), although some negative reports exist (39). One study specifically examined diffusion imaging measures within the hippocampus to show increased fractional anisotropy (FA) and decreased mean diffusivity (MD) after ECT, but connections to and from the hippocampus and relationships with clinical response were not examined (40).

Despite neuroimaging evidence that ECT elicits structural and functional neuroplasticity in the hippocampus and its circuitry, dissociating neural effects associated with clinical outcome from effects associated with seizure therapy itself has been more challenging. For example, recent meta-analyses (29,30) and mega-analyses (41) have failed to find positive associations between observed hippocampal volume enlargements and symptom improvement. These observations suggest that response mechanisms occurring at the microscale may not be detectable with gross volume measurements or may be masked by larger effects attributable to electrical stimulation.

It is also possible that more regional changes in hippocampal structure and connectivity might contribute to clinical response. The anterior hippocampus (ventral hippocampus in rodents) has more concentrated projections to prefrontal cortex as well as the amygdala, nucleus accumbens, bed nucleus of stria terminalis, and regions of the hypothalamic-pituitary-adrenal axis (42). Hippocampal connections are topographically organized; afferents (either directly or by way of the entorhinal cortex) and efferents, which mediate stress, emotion, and affect, are located more anteriorly (42–44). Though ECT-related changes appear to encompass most hippocampal subfields (25), effects appear pronounced in the right anterior hippocampus (31). ECT-related increases in regional cerebral blood flow are also observed in the right anterior hippocampus (45), and right hippocampal functional connectivity is shown to distinguish ECT responders and nonresponders (25). However, whether variations in the structural connectivity from the right or left anterior hippocampus occur with ECT and relate to clinical response is not yet known.

To test the hypothesis that anterior hippocampal structural connectivity relates to ECT response, the current study used diffusion magnetic resonance imaging (MRI) and probabilistic tractography from patients with major depression who underwent scanning before and after an index treatment series of ECT. To determine whether diffusion tensor metrics and tract volume change with treatment and differ in ECT responders and nonresponders and control subjects without depression, functionally defined seeds centered in the right and left anterior hippocampus were tracked to all other connected brain voxels. To address if hippocampal connectivity represents a biomarker of clinical outcome, pretreatment diffusion imaging measures were also compared between clinical responders and nonresponders to ECT.

METHODS AND MATERIALS

Subjects

Patient participants (n = 36, 20 women, mean age 41.49 years ± 13.57 SD) experiencing a major depressive episode as defined by DSM-IV were recruited from individuals scheduled to receive ECT at the Stewart and Lynda Resnick Neuropsychiatric Hospital at University of California, Los Angeles, as part of their treatment plan. All patient participants were considered to have treatment-resistant depression, defined as lack of response to at least two antidepressant drug trials for at least 4 to 6 weeks each and a current depressive episode lasting at least 6 months or longer. Patients with schizophrenia spectrum disorders and dementia, current psychosis, first-episode depression, depression onset after 50 years of age or related to a medical illness, substance abuse within 6 months, and previous neuromodulation therapy within 6 months of current ECT treatment were excluded.

Patients underwent MRI scans and clinical assessments at baseline (within 48 hours of the first ECT session) and within a week of completing the clinically determined ECT index treatment series (approximately 4–5 weeks later). A sex-matched and age-matched group of healthy control subjects (n = 32, 17 women, mean age 39.34 years ± 12.27 SD) were scanned using the same MRI sequences at an interval similar to the before and after ECT assessments (approximately 4 weeks). All participants provided informed consent approved by the University of California, Los Angeles, Institutional Review Board. Demographic and clinical characteristics of subjects are summarized in Table 1. Overlapping subjects have been investigated in previous studies of brain structure and functional connectivity with ECT (27,28,31,46) and in a prior whole-brain voxel-based diffusion MRI tract-based spatial statistics (47) study, which included 59% of the subjects examined in the present study (36).

Clinical Measures

The 17-item Hamilton Depression Rating Scale (HAM-D) (48) and Montgomery–Åsberg Depression Rating Scale (49) were used to track symptoms before and after ECT. Owing to the high correlation between these mood scales, the HAM-D was chosen as the primary measure of clinical outcome and used to determine response criteria for depressive symptoms. Response status was defined as >50% reduction of

Table 1. Sample Characteristics

	Patients (n = 36)		Control Subjects (n = 32)
	Nonresponders (n = 17)	Responders (n = 19)	
Age, Years, Mean (SD)	40.65 (11.17)	42.32 (15.97)	39.34 (12.27)
Male/Female, n	5/12	11/8	15/17
Baseline HAM-D, Mean (SD)	23.06 (4.71)	25.42 (5.26)	–
Post-ECT HAM-D, Mean (SD)	19.06 (4.94)	7.58 (3.36)	–
Percent Right Unilateral ECT	69.88%	98.37%	–

ECT, electroconvulsive therapy; HAM-D, Hamilton Depression Rating Scale.

depressive symptoms in the HAM-D from baseline to post-treatment in accordance with prior studies (50).

Electroconvulsive Therapy

ECT protocols included the seizure threshold titration method, and 5 to 6 times seizure threshold was delivered using right unilateral (RUL) d'Elia electrode placement with an ultra-brief pulse width of 0.3 ms. Of patients, 67% received exclusively RUL ECT throughout the index series. As based on clinical determination, electrode placement was switched to bilateral placement during the index series for the remaining patients. In this subgroup, bilateral ECT was delivered using 1.5 times seizure threshold with a brief pulse width of 0.5 ms. Established MECTA spECTrum Q (MECTA Corporation, Tualatin, OR) parameter protocols for ultra-brief and brief pulse ECT (according to electrode placement) were applied, and other dose parameters were adjusted to produce an adequate seizure duration and amplitude on electroencephalography depending on individual patient characteristics. ECT was administered 3 times weekly, and the length of the ECT index series was determined for each patient based on clinician-evaluated response. The average number of ECT sessions for all patients was 11.6 (SD 2.6; range, 6–18). ECT administration was performed using methohexital (1 mg/kg) and succinylcholine (1 mg/kg). ECT (5000Q; MECTA Corporation) was induced in an inpatient setting at the Stewart and Lynda Resnick Neuropsychiatric Hospital, University of California, Los Angeles.

Image Acquisition

All participants underwent scanning on a Siemens 3T Allegra MRI system (Siemens Healthcare GmbH, Erlangen, Germany) using diffusion-weighted imaging at each time point. Scanning included a spin echo–echo planar sequence with 61 noncollinear, icosahedrally distributed directions, 10 b0 images, and 55 axial slices (repetition time = 7300 ms; echo time = 95 ms; b = 1000 s/mm^2; field of view = 24 cm; 96 × 96 matrix; voxel size = 2.5 mm^3). In addition, a structural multiecho magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence with real-time motion correction was acquired to facilitate registration to a standard template (repetition time = 2530 ms; echo times = 1.74 ms; 3.6 ms, 5.46 ms, 7.32 ms; inversion time = 1260 ms; FA = 7°; field of view = 256 × 256 mm; matrix = 256 × 192; voxel size = 1.3 × 1 × 1 mm).

Image Processing

Image data were processed using FSL software version 5.0.10 (FMRIB Software Library, Oxford, United Kingdom). All diffusion scans were visually inspected for motion, signal dropout, gross anatomic abnormalities, and registration failure before inclusion. First, diffusion data were coregistered to the b0-weighted images and preprocessed to correct for residual eddy current distortions (51,52). DTIFIT, part of FSL's Diffusion Toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT), was used to fit an ellipsoid tensor at each voxel. Diffusion data were then registered to the high-resolution MPRAGE images acquired in the same session and subsequently to a 2-mm^3 standard Montreal Neurological Institute (MNI) 152 atlas (53).

In MNI atlas space, a functionally defined hippocampal seed region centered in the anterior hippocampus was chosen based on coordinate locations identified from our prior observations of increased regional cerebral blood flow (45) as well as more pronounced anterior hippocampal volume increases (31) in association with ECT. This seed region included a sphere with a 5-mm radius and center of mass located at coordinates x = 26.5, y = −16.5, z = −16.5 in MNI space (Figure 1). The same coordinates were used for the left hemisphere anterior hippocampus with the exception of the x dimension (x = −26.5).

The MNI coordinates for seed placement were then mapped back to individual diffusion space using inverse transformations on a per subject/time basis for hippocampal tractography (53). The probability distribution of primary fiber orientations was first estimated at each voxel using Markov chain Monte Carlo sampling in FSL's BEDPOSTX tool (54). Probabilistic tractography was performed using PROBTRACKX (55), which extracted fiber distributions from the seeds to other brain voxels. Default PROBTRACKX parameters were used: seeding from mask, 5000 samples, curvature threshold of 0.2, and a skull-stripped brain mask to constrain results to inside the brain.

To measure tract volume, the outputs of PROBTRACKX2 were divided by the total number of fibers (termed waytotal) for normalization across subjects, thresholded at 0.001 (56), and binarized. Voxel counting then estimated tract volume for use as a dependent measure statistical analysis. Other tract-dependent measures included FA and axial diffusivity (AD) (λ_1), radial diffusivity (RD) [($\lambda_2+\lambda_3$)/2], and MD [($\lambda_1+\lambda_2+\lambda_3$)/3]. To ensure that diffusion parameters were extracted from white matter, FSL's tract-based spatial statistics analysis pipeline (47) was used to generate a white matter mask from the group-averaged FA map (thresholded at 0.2). This mask was transformed back to individual diffusion space to constrain the measurement of diffusion metrics (FA, AD, RD, and MD) in each dataset. Figure 2 shows three-dimensional views of group-averaged probabilistic tractography from the anterior

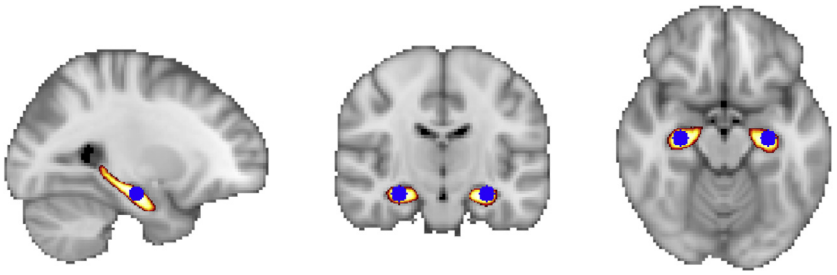

Figure 1. Hippocampal seed placement. Seeds were placed in the anterior hippocampus in the right (x = 26.5, y = −16.5, z = −16.5) and left (x = −26.5, y = −16.5, z = −16.5) hemispheres in Montreal Neurological Institute standard space, and seeds (5-mm radius) were then transformed into individual native diffusion space for tractography to all other brain voxels. Seed regions are shown in blue. Red-yellow mask shows probabilistic atlas of right and left hippocampus thresholded at 50% for visibility.

hippocampus and two-dimensional slice views of tractography both with and without the white matter mask.

Statistical Analysis

All statistical analyses were performed with IBM SPSS Statistics for MAC, Version 25.0 software (IBM Corp., Armonk, NY). Dependent measures included tract volume as well as FA, MD, AD, and RD extracted from anterior hippocampal tracts in each hemisphere, subject, and time point. These measures were used to examine the longitudinal effects of ECT and effects of clinical response including time (baseline, posttreatment) as a within-subjects factor and response status (responder, nonresponder) as a between-subjects factor with general linear mixed models (GLMMs). Significant time-by-response group interactions were followed by examining effects of time in each response group separately. Though response categorization is used in clinical and research practice for determining treatment decisions and efficacy and interpreting the potential clinical utility of biological measures (57–60), thresholds are somewhat arbitrary and can produce statistical biases (61,62). Relationships between dependent measures showing significant change with treatment in the GLMMs and continuous change in HAM-D scores were thus also evaluated in post hoc analyses.

To establish potential moderating effects of pretreatment hippocampal structural connectivity on subsequent clinical response, associations between baseline diffusion measures with change in HAM-D scores were examined using the general linear model. The general linear model also compared diffusion measures between patients and control subjects at baseline to determine normative values and main effects of diagnosis. Finally, to establish the variance associated with repeated measures, the GLMM was used to compare differences across time in control subjects.

GLMM and general linear model analyses included sex, age, and percent RUL lead placement (for the ECT cohort) as covariates. Means for each dependent measure by time point, response status, and diagnosis are reported in Table 2. Considering each diffusion measure as a separate hypothesis regardless of hemisphere, main effects of ECT were considered significant using a threshold of $p < .01$ (Bonferroni correction for five independent tests—FA, MD, RD, AD, and tract volume). However, as smaller effects that distinguish response groups may still be clinically informative, a less conservative uncorrected p value of $< .05$ was used as the statistical threshold for time-by-response interactions and for post hoc tests examining relationships with change in mood examined as a continuous variable.

RESULTS

Patients and control subjects did not differ significantly in age ($F_{1,67} = 0.47$, $p = .49$) or sex ($\chi^2_{1,68} = 0.40$, $p = .52$) distributions. Of patients receiving ECT, 53% (19/36) were defined as

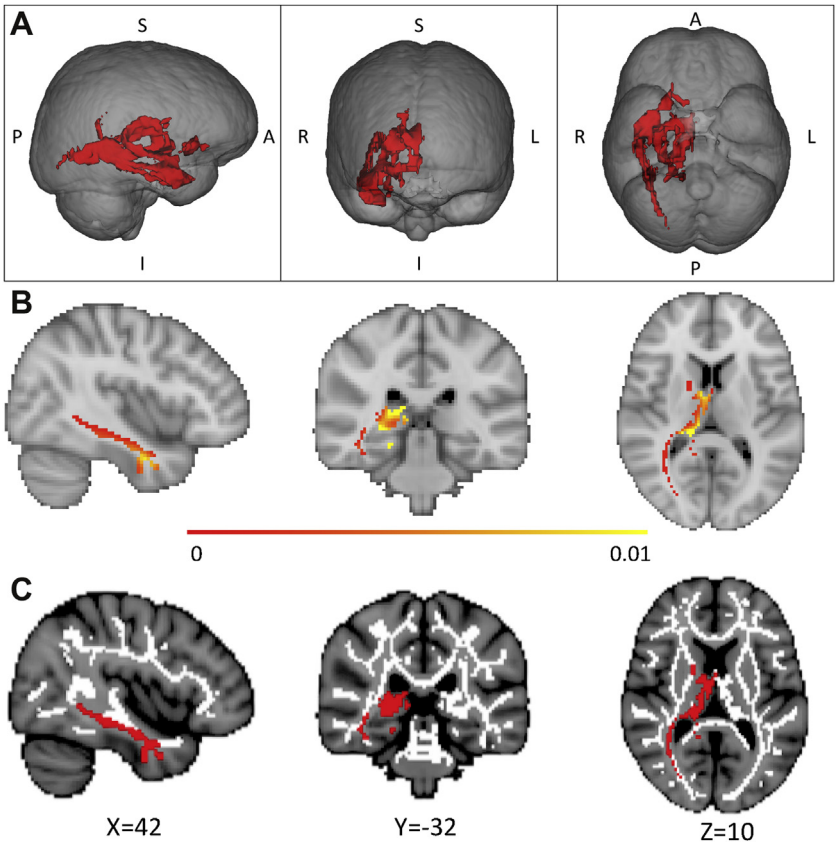

Figure 2. **(A–C)** Hippocampal tractography. Three-dimensional views of group-averaged probabilistic tractography from the anterior hippocampus seed shown for the right hemisphere **(A)** and two-dimensional slice views of anterior hippocampus probabilistic tractography illustrated in a single subject both without **(B)** and with **(C)** the binarized group averaged white matter mask used to constrain measurement of average diffusion metrics in a diffusion dataset. A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

Table 2. Within-Group Comparisons Across Time for the Left and Right Hippocampal Tracts and Each Diffusion Metric and Volume

	Right Hippocampal Tracts				Left Hippocampal Tracts			
	Baseline, Mean (SD)	Follow-up, Mean (SD)	Time, *F*, *p*	Effect Size, η_p^2	Baseline, Mean (SD)	Follow-up, Mean (SD)	Time, *F*, *p*	Effect Size, η_p^2
Axial Diffusivity								
All patients (*n* = 36)	12.99 (1.16)	12.72 (1.11)	9.13, .005[a]	.216	13.08 (0.69)	13.0 (0.80)	1.18, .28	.001
Nonresponders (*n* = 17)	12.82 (1.33)	12.74 (1.36)	0.458, .51	.032	13.03 (0.78)	12.92 (0.89)	0.175, .68	.103
Responders (*n* = 19)	13.13 (1.01)	12.70 (0.85)	13.51, .002[a]	.475	13.12 (0.62)	13.07 (0.72)	0.041, .84	.056
Control subjects (*n* = 32)	12.98 (1.10)	12.52 (1.71)	1.71, .20	.038	12.95 (0.39)	12.85 (0.59)	0.594, .44	.019
Radial Diffusivity								
All patients	8.28 (1.14)	8.07 (1.11)	7.58, .009[a]	.194	8.27 (0.60)	8.22 (0.62)	0.658, .42	.006
Nonresponders	8.20 (1.30)	8.16 (1.34)	0.203, .66	.015	8.31 (0.77)	8.82 (0.69)	0.294, .59	.135
Responders	8.36 (1.01)	8.0 (0.87)	11.98, .003[a]	.459	8.22 (0.41)	8.82 (0.58)	0.022, .88	.008
Control subjects	8.33 (1.02)	7.96 (1.75)	1.13, .30	.039	8.13 (0.49)	8.23 (0.47)	1.11, .30	.035
Mean Diffusivity								
All patients	9.85 (1.14)	9.61 (1.11)	8.49, .006[a]	.211	9.87 (0.61)	9.81 (0.66)	0.878, .36	.004
Nonresponders	9.74 (1.30)	9.68 (1.34)	0.291, .60	.021	9.89 (0.76)	9.76 (0.73)	0.263, .61	.164
Responders	9.95 (1.01)	9.55 (0.87)	12.96, .002[a]	.483	9.86 (0.45)	9.86 (0.61)	0.050, .83	.020
Control subjects	9.88 (1.04)	9.48 (1.75)	1.32, .26	.046	9.74 (0.44)	9.77 (0.48)	0.119, .73	.004
Fractional Anisotropy								
All patients	0.320 (0.004)	0.320 (0.004)	0.169, .68	.006	0.325 (0.003)	0.320 (0.004)	1.24, .27	.034
Nonresponders	0.318 (0.006)	0.316 (0.007)	0.938, .35	.068	0.340 (0.005)	0.327 (0.004)	0.166, .69	.012
Responders	0.323 (0.006)	0.324 (0.005)	0.165, .69	.010	0.320 (0.003)	0.321 (0.005)	1.17, .29	.063
Control subjects	0.318 (0.004)	0.321 (0.005)	0.429, .52	.014	0.326 (0.005)	0.316 (0.004)	2.86, .10	.086
Volume								
All patients	7022 (260)	6954 (336)	0.071, .79	.002	7328 (265)	7092 (308)	0.771, .39	.026
Nonresponders	6502 (264)	6624 (429)	0.138, .72	.009	7019 (367)	6715 (387)	0.610, .45	.043
Responders	7488 (411)	7251 (472)	0.372, .55	.026	7605 (352)	7429 (367)	0.212, .65	.018
Control subjects	6763 (348)	6491 (356)	1.46, .24	.048	7076 (354)	7047 (227)	0.015, .90	.001

p values reflect changes across time (before and after electroconvulsive therapy for all patients [*n* = 36], treatment responders [*n* = 19] and nonresponders [*n* = 17] and baseline to follow-up for control subjects [*n* = 32]) for axial diffusivity, radial diffusivity, and mean diffusivity as well as fractional anisotropy and tract volume. Results were obtained using the general linear model including subject as a within-subjects measure and age and sex as covariates. In addition, percent of right unilateral sessions received was included as a covariate for all patient comparisons. Axial diffusivity, radial diffusivity, and mean diffusivity are multiplied by 10,000 to scale to integers, whereas fractional anisotropy and volume are unscaled. η_p^2 is used as a measure of effect size, which partials out the effects of other variables in the model.

[a]Significant effects.

treatment responders (i.e., showed >50% change in HAM-D ratings over the course of ECT). Groups defined by response status also did not differ in age ($F_{1,35}$ = 0.13, p = .72) or sex ($\chi^2_{1,36}$ = 2.95, p = .083).

Significant main effects of ECT were observed for right hippocampal tract AD ($F_{1,35.01}$ = 9.13, p = .005, η_p^2 = .22), RD ($F_{1,35.27}$ = 7.58, p = .009, η_p^2 = .19), and MD ($F_{1,35.31}$ = 8.49, p = .006, η_p^2 = .21). However, time-by-response interactions were also observed for these same measures (AD: $F_{1,34.33}$ = 4.31, p = .045, η_p^2 = .08, RD: $F_{1,34.22}$ = 4.56, p = .04, η_p^2 = .06, MD: $F_{1,34.26}$ = 4.81, p = .035, η_p^2 = .07). Follow-up analyses in response groups examined separately revealed that only individuals responding to ECT showed significant changes in AD, RD, and MD after completing the ECT index (all $p < .01$; statistical details provided in Table 2), whereas metrics remained stable in nonresponders (all $p > .05$). Post hoc analyses confirmed significant correlations between change in AD, RD, and MD and change in HAM-D ratings examined continuously (AD: r = .34, p = .004, RD: r = .40, p = .001, MD: r = .38, p = .001). Figure 3 shows mean AD, RD, and MD for responders and nonresponders at each time point. Figure 4 shows relationships between change in each diffusion metric and change in mood.

Significant changes across time and response-by-time interactions were not observed for right hippocampal tract FA or tract volume (Table 2). Furthermore, no diffusion metric showed significant main effects of time or time-by-response interactions for left hippocampal pathways (Table 2). Associations between baseline measures of structural connectivity were not found to be significantly associated with the extent of clinical response to ECT (all $p > .05$). No significant differences in the five structural connectivity metrics were found between patients and control subjects compared at baseline (all $p > .05$), and neither of the two dependent measures changed significantly over time in control subjects undergoing scanning at two intervals (Table 2).

DISCUSSION

The relatively high response rates and rapid effects of ECT (4,63) provide a valuable opportunity to target biomarkers

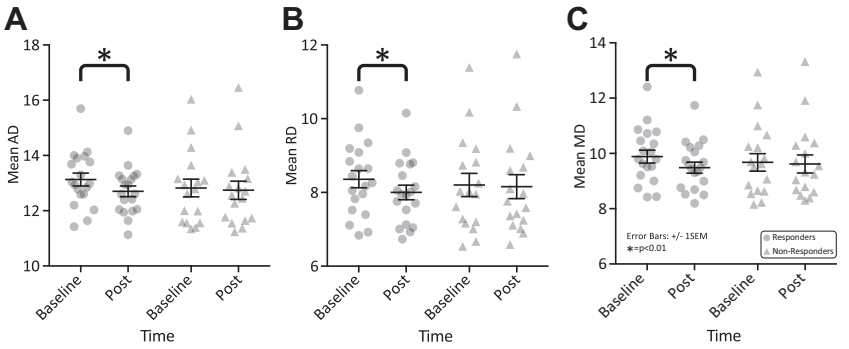

Figure 3. Mean axial diffusivity (AD) **(A)**, radial diffusivity (RD) **(B)**, and mean diffusivity (MD) **(C)** in electroconvulsive therapy responders and nonresponders at each time point. Values of diffusion metrics have been multiplied by 10,000 to scale values as integers. Individual data points are plotted along with means ± 1 SD. *Significant differences ($p < .01$) between baseline and post–electroconvulsive therapy in treatment responders.

and mechanisms underlying antidepressant response over shorter intervals that are expected to coincide with other treatments for major depression. The hippocampus, which is interconnected with cortical association areas, the amygdala, septal area, hypothalamus, thalamus, striatum, and monoaminergic cell masses in the brainstem via the entorhinal cortex, subicular complex, or fornix, is widely implicated in depression (19,20,64) and its treatment (65,66). This study sought to investigate whether indices of white matter structural connectivity in anterior hippocampal circuits—which are specifically associated with anxiety, stress, affect, and integration of emotional valence in perception, imagination, and recall (42,67–69)—relate to ECT clinical outcome. Using probabilistic tractography methods, our results showed that ECT induces significant changes in the microstructure of hippocampal white matter pathways in the right hemisphere. These effects distinguish treatment responders from nonresponders (Figure 3) and relate to the extent of clinical response (Figure 4). Though measures did not differ statistically when comparing patients before treatment with control subjects without depression, posttreatment means changed in the direction of control values, suggesting some normalization of hippocampal connectivity with ECT. Pretreatment structural connectivity measures did not relate to the extent of symptom improvement. These results suggest that changes in anterior hippocampal structural connectivity act as a biomarker, though less as a pretreatment predictor, of antidepressant response to ECT.

In this study, AD, RD, and MD, but not FA, were shown to change in anterior hippocampal pathways with ECT. Although FA, representing the magnitude of directional diffusion in a voxel, is the most commonly used summary index of white matter integrity, other diffusivity measures may be more sensitive to underlying pathophysiology (70–72). AD, which represents diffusion parallel to axonal fibers, is considered a marker of axonal integrity, although both increases and decreases may indicate white matter changes and pathology (70–72). RD, which measures diffusion perpendicular to axonal fibers, is considered a marker of myelin integrity and can signify changes in axonal diameter or density. MD, measuring the rotationally invariant magnitude of diffusion, is sensitive to membrane density, cellularity, tissue atrophy, and edema (70–72). Notably, as FA is a nonspecific measure of diffusion quantified from all diffusion tensor eigenvalues, changes in other diffusion metrics can occur without significant changes in FA. Indeed, our study results showed that although hippocampal tract FA remained relatively stable before and after ECT, AD, RD, and MD all exhibited pronounced decreases over the course of the ECT index series. Because these changes were specific to treatment responders, results suggest that the possible underlying biological processes underlie therapeutic response and do not simply reflect physiological effects related to the stimulation procedures of ECT.

Preclinical studies suggest that hippocampal neuroplasticity, which includes neurogenesis, synaptogenesis, dendrogenesis, and angiogenesis, has an important role in

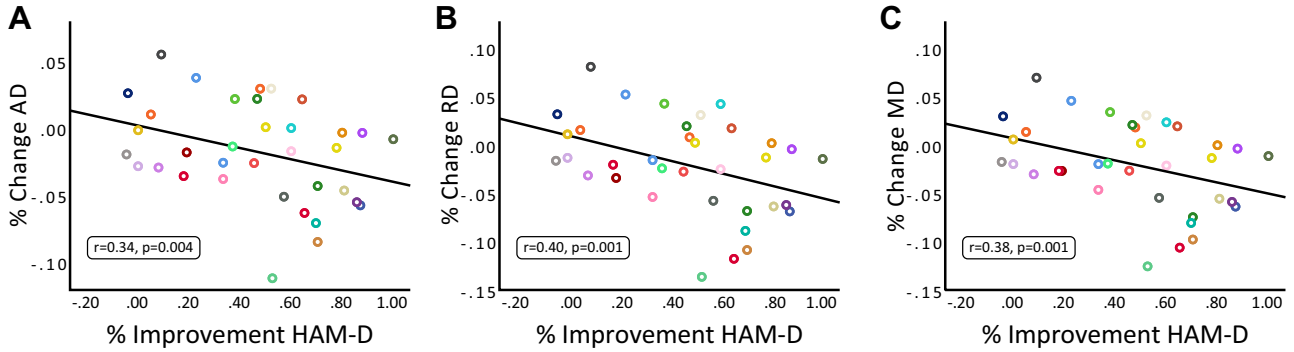

Figure 4. Scatterplots showing significant relationships between change in diffusion metrics and change in Hamilton Depression Rating Scale (HAM-D). Associations between axial diffusivity (AD) **(A)**, radial diffusivity (RD) **(B)**, and mean diffusivity (MD) **(C)** changes and change in HAM-D are shown in each panel. One outlier with a 42% deterioration in HAM-D during the course of electroconvulsive therapy was removed for analysis.

antidepressant response (73–76). For example, reduced hippocampal neurogenesis observed in animal models of depression (77–80) can be reversed by antidepressant treatment (81–84) and particularly by electroconvulsive shock (ECS) (85–87). However, the extent of adult neurogenesis in the adult human brain remains debated (74,88). Furthermore, proliferation of neural progenitor cells in the hippocampus may have little effect or only indirect effects on hippocampal structural connectivity, even though some new neurons are integrated into functional circuitry, and a reorganization of synapses and neural connections occurs (74).

At the same time, animal studies also show that ECS elicits an upregulation of hippocampal glial and endothelial cell proliferation and density (76,89,90). Specifically, with regard to glial cells, markers of proliferating astrocytes, microglia, and NG2 cells have been observed following ECS (89–92). Further, ECS is also shown to overcome inhibition of gliogenesis (93). As many of these same studies show that glia activation and proliferation occur in the hippocampus but are also shown as present in white matter, it is possible that such ECT-induced cellular events could influence MRI diffusion metrics. Because NG2 cells are equated as oligodendrocyte precursor cells and can differentiate into oligodendrocytes, NG2 cells may have a larger contribution to the observed hippocampal white matter connectivity effects (94). Notably, it has been shown that NG2 cells play an important role in remyelination and influence axonal growth (94), thus potentially affecting both AD and RD. Interestingly, it has also been demonstrated that neuron-NG2 glial transmission in the hippocampus elicited by theta burst stimulation is analogous to long-term potentiation, a key feature of neuronal plasticity, and involves alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (95). Of potential relevance, the antidepressant effects of subanesthetic ketamine administration, which, similar to ECT, also elicits a rapid clinical response, may similarly involve downstream alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid signaling (66,96).

Neurotrophic factors (proteins responsible for the growth, survival, and maintenance of neurons and glia) underlie neuroplasticity. Cumulating evidence supports that neurotrophic factors, including but not limited to brain-derived neurotrophic factor and vascular endothelial growth factor, are modulated by typical antidepressants (97,98) and ECT (85,99,100). In parallel, specific aspects of immune system function are implicated in depression pathophysiology (101,102) and are directly affected by ECT (103). That is, at least transiently, ECT is shown to increase the expression of particular proinflammatory cytokines, such as tumor necrosis factor alpha, interleukin-1β, and interleukin-6 (103–105). Relevant to inflammation and immune system cytokine response, animal studies have also shown increased activation of microglia as well as other macrophages following ECS in the hippocampus and other parts of the central nervous system (92,103). Notably, immune response and neurotrophic processes are shown to interact, such that neurotrophic factors can upregulate microglia activation, which can in turn modulate cytokine expression with downstream effects on monoaminergic neurotransmission (105). Preclinical studies suggest that structural and functional features of cortical and subcortical structures, including the hippocampus, are linked with inflammatory response (106). Moreover, human studies have shown relationships between inflammatory response and brain structure (107) or functional connectivity (108) in depression. Because inflammation is associated with changes in extracellular and intracellular fluid as well as other reactive cellular microevents, these factors could likewise account for changes in the microstructural integrity (AD, RD, and MD) of hippocampal white matter tracts observed following ECT.

In this study, changes in hippocampal white matter connectivity were detected in the right, but not the left, hemisphere. When modeling ECT electrical fields, current density is shown to be greater proximal to the electrode site such that RUL ECT leads to more focal stimulation and bilateral ECT produces more diffuse brain electrical fields (109,110). A recent mega-analysis of hippocampal volume change in ECT also demonstrated in vivo that RUL leads to more rightward volume change, whereas volume change is similar in both hemispheres with bilateral stimulation (41). In the current study, the majority of patient participants received RUL ECT (67%) and 84% of all ECT sessions administered were RUL. Thus, although electrode placement was included as a covariate in statistical analyses, it is possible that greater lateralized RUL dose of stimulation led to more structural plasticity in right hippocampal pathways. These findings are consistent with prior ECT imaging studies including predominately RUL stimulation that have also shown more rightward ECT effects (25,31). However, also of note, depression has been suggested to be associated with a hemispheric imbalance (111), and some aspects of emotional processing might be more lateralized to the right hemisphere (112) to provide a biological basis for right hemisphere therapeutic effects.

Some limitations to the current investigation should be taken into account. First, this was a naturalistic study, so ECT parameters were not experimentally controlled. Consequently, we were not able to evaluate effects of particular treatment variables, such as lead placement, which may impact the laterality of findings. Though diffusion imaging parameters used for this study (including 61 gradient diffusion directions, 2.5-mm^3 voxel size) were deemed sufficient to address hypotheses, more recent advances in MRI software and hardware will allow for greater precision and accuracy of measurements. While diffusion MRI is sensitive to neurobiological changes that may occur with treatment, the selectivity of this measurement technique still lacks ground truths. Thus, changes in fiber coherence, integrity, or myelination can only be inferred based on supporting literature and are still subject to some interpretation.

Conclusions

To our knowledge, no prior studies to date have examined structural connectivity from the hippocampus to connected brain regions following ECT in depression. Our findings suggest that therapeutic response involves neuroplastic changes in the fiber connections between the hippocampus and other brain regions, where such neuroplastic processes differentiate treatment responders from nonresponders. Hippocampal structural connectivity may thus have a bearing on treatment management in individual patients and serve as a biomarker for novel treatment approaches. In the context of the animal

literature and based on the time scale of change, the mechanisms driving changes in hippocampal structural connectivity might be due to an ECT-induced glial response, including NG2 cells and microglia in particular. Furthermore, as reductions in both AD and RD were observed in responders, the neurobiological effects appear more consistent with an increase in cellular density and axonal changes than myelination, though all may still occur. Future studies leveraging more advanced diffusion MRI acquisition and analysis techniques, which include other biomarkers such as gene expression and measures of inflammatory response, may provide further insight into the antidepressant mechanisms of ECT and potentially other antidepressant therapies.

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