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Volume of the Human Hippocampus and Clinical Response Following Electroconvulsive Therapy

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ABSTRACT

BACKGROUND: Hippocampal enlargements are commonly reported after electroconvulsive therapy (ECT). To clarify mechanisms, we examined if ECT-induced hippocampal volume change relates to dose (number of ECT sessions and electrode placement) and acts as a biomarker of clinical outcome.

METHODS: Longitudinal neuroimaging and clinical data from 10 independent sites participating in the Global ECT-Magnetic Resonance Imaging Research Collaboration (GEMRIC) were obtained for mega-analysis. Hippocampal volumes were extracted from structural magnetic resonance images, acquired before and after patients (n = 281) experiencing a major depressive episode completed an ECT treatment series using right unilateral and bilateral stimulation. Untreated nondepressed control subjects (n = 95) were scanned twice.

RESULTS: The linear component of hippocampal volume change was 0.28% (SE 0.08) per ECT session ($p < .001$). Volume change varied by electrode placement in the left hippocampus (bilateral, 3.3 ± 2.2%, d = 1.5; right unilateral, 1.6 ± 2.1%, d = 0.8; $p < .0001$) but not the right hippocampus (bilateral, 3.0 ± 1.7%, d = 1.8; right unilateral, 2.7 ± 2.0%, d = 1.4; p = .36). Volume change for electrode placement per ECT session varied similarly by hemisphere. Individuals with greater treatment-related volume increases had poorer outcomes (Montgomery–Åsberg Depression Rating Scale change –1.0 [SE 0.35], per 1% volume increase, p = .005), although the effects were not significant after controlling for ECT number (slope –0.69 [SE 0.38], p = .069).

CONCLUSIONS: The number of ECT sessions and electrode placement impacts the extent and laterality of hippocampal enlargement, but volume change is not positively associated with clinical outcome. The results suggest that the high efficacy of ECT is not explained by hippocampal enlargement, which alone might not serve as a viable biomarker for treatment outcome.

Keywords: Antidepressant response, Biomarker, Brain, Depression, ECT, Neuroimaging

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Major depression is the leading cause of disability worldwide (1), yet standard treatments for depression are only moderately successful (2). There is thus a need to better understand the mechanisms of successful response to antidepressant therapies, which may then inform more effective treatment interventions for patients with major depression. Though depression is typically treated with different forms of psycho- or pharmacotherapies, electroconvulsive therapy (ECT) is still regarded as the most effective acute treatment for severe and treatment-resistant major depressive episodes (3). With ECT, electrical current is applied through scalp electrodes, intentionally inducing a seizure, typically two or three times per week. When administered with modern techniques under anesthesia, ECT is well tolerated and has a good safety record. Yet despite its safety and efficacy (3), the neurobiological underpinnings of ECT response, as with other forms of antidepressant treatment, remain unclear. Establishing objective biomarkers of clinical response could allow for the timely implementation of alternative treatment strategies in unresponsive patients.

Most neuroimaging studies of ECT demonstrate treatment-related volume increase of the hippocampus (4–9), which suggests that hippocampal volume may serve as a biomarker of clinical response. These observations together with data from preclinical studies are taken as evidence to support the neurogenic theory of depression (10). In particular, translational models provide evidence to suggest that a decrease of adult neurogenesis in the hippocampus is associated with depression and can potentially be reversed with ECT (10–12). This hypothesis is supported by observations that the human

SEE COMMENTARY ON PAGE e59

hippocampus harbors neuronal stem cells that proliferate throughout life (13), that the volume of the hippocampus is frequently reported to be reduced in depression (14), and that in an animal model of ECT, a dose-dependent increase in neurogenesis is seen (15). However, the mechanisms underlying ECT-related volume enlargement of the human hippocampus remain unclear, and associations with clinical outcome have not been conclusively demonstrated (9).

In ECT practice, the number of treatments in an ECT index series typically depends on the severity of depression and speed of recovery, such that unresponsive patients tend to receive more ECT sessions on average (16). Bilateral (BL) electrode placement is widely used for stimulation. However, to mitigate the risk of cognitive side effects, particularly for verbal and retrograde autobiographical memory, the use of other electrode montages is also standard practice (17–19). In particular, right unilateral (RUL) ECT, which was developed in an effort to reduce the spread of seizure activity to brain areas such as the left temporal cortex, which is important for verbal memory, is often used as a first-line form of ECT (17,18). Computational modeling of electric fields supports that bilateral ECT leads to more diffuse brain stimulation than more focal RUL ECT (20,21). Both the number of ECT sessions received and electrode placement may thus impact the extent and laterality of hippocampal neuroplasticity and in turn the mechanisms of treatment response. However, previous studies have lacked the sample sizes and statistical power needed to investigate the moderating effects of these parameters or have simply controlled for these factors as nuisance variables. Consequently, no clear associations between dose or mode of electrode placement and measured hippocampal structural changes have emerged (12,22,23).

To address the clinical relevance of ECT-related hippocampal volume change, we included 281 patients from the Global ECT-Magnetic Resonance Imaging Research Collaboration (GEMRIC) (24) and analyzed volume changes of the hippocampus after serial ECT treatment. With the largest and most geographically diverse sample to date, and by using an optimized image processing pipeline, we obtained sufficient statistical power to probe for relationships between hippocampal volume, dose response (number of sessions as well as electrode placement), and symptom improvement of relatively small effects (24) (Cohen's $f^2_{1,280} = 0.03$, $\alpha = .05$, power = 0.80, as estimated for a linear model). Changes in hippocampal volume in untreated nondepressed control subjects scanned at two different time points were also assessed to estimate the variance associated with repeated measures over time.

METHODS AND MATERIALS

Participants

The clinical and demographic characteristics of the GEMRIC sample are summarized in Table 1 and detailed in Oltedal *et al.* (24). Data from 10 sites were available, including 281 patients (59.8% female, mean age ± SD, 54.8 ± 16.4 years) and 95 healthy control subjects (60% female, mean age ± SD, 46.9 ± 14.6 years). Patients were scanned before and after ECT, and control subjects were scanned at two time points without receiving ECT. Due to some missing data points (e.g., follow-up scan, number of ECTs, or depression score), the sample sizes for the statistical models used to test for the effects of ECT number or relationships with clinical outcome ranged from 250 to 268 patients. ECT practice varied among contributing sites in terms of electrode placement and/or stimulation parameters as detailed previously (24). Concurrent psychotropic medications were used at most sites, as described in the Supplement. To test for the effects of electrode placement, only patients that received exclusively RUL (n = 149) or BL (n = 50; 10 bifrontal and 40 bitemporal) treatment throughout all sessions of the ECT index series were included for analysis. All sites' contributing data received approval by their local ethical committees or institutional review board, and the centralized mega-analysis was approved by the Regional Ethic Committee South-East in Norway (2013/1032 ECT and Neuroradiology, June 1, 2015).

Table 1. Clinical and Demographic Characteristics of the GEMRIC Sample

Subject Characteristics	Mean ± SD	n[a]
Control Subjects		
Age, years	46.9 ± 14.6	95
Baseline right hippocampal volume, mm^3	4052.5 ± 446.2	95
Change in right hippocampal volume, %	0.05 ± 0.8	95
Baseline left hippocampal volume, mm^3	3948.0 ± 444.3	95
Change in left hippocampal volume, %	0.01 ± 0.7	95
Baseline intracranial volume, cm^3	1520.2 ± 179.2	95
Patients		
Age, years	54.9 ± 16.4	281
Baseline right hippocampal volume, mm^3	3774.1 ± 588.3	254[b]
Change in right hippocampal volume, %	2.9 ± 1.9	250[c]
Baseline left hippocampal volume, mm^3	3657.9 ± 561.0	254[b]
Change in left hippocampal volume, %	2.2 ± 2.3	250[c]
Baseline intracranial volume, cm^3	1505.9 ± 175.6	254[b]
Baseline depression score	33.3 ± 8.2	279
Posttreatment depression score	15.0 ± 11.0	277
Duration of episode, months	20.1 ± 31.6	158
No. of ECTs, total	12.0 ± 5.2	273[d]
BL only	14.6 ± 7.5	50
RUL only	10.9 ± 3.6	149
No. of ECTs, responders	11.5 ± 5.3	166
No. of ECTs, nonresponders	13.2 ± 4.7	102

BL, bilateral; ECT, electroconvulsive therapy; GEMRIC, Global ECT-MRI Research Collaboration; RUL, right unilateral.

[a]The number of subjects vary because of missing data for some variables.

[b]A total of 27 subjects were missing magnetic resonance imaging either before or after treatment (baseline volume is not reported for these subjects).

[c]Four subjects failed automated processing of volume change.

[d]Information about number of ECTs was missing for 8 subjects; some subjects received more than one form of lead placement and one subject also received left anterior right temporal stimulation.

Image Acquisition and Postprocessing

The image processing methods have been detailed previously (24). Briefly, T1-weighted magnetic resonance imaging volumes with a minimal resolution of 1.3 mm in any direction were acquired before and after (typically within 1–2 weeks) an ECT

treatment series using 1.5T (1 site) or 3T (9 sites) scanners. Raw structural magnetic resonance imaging data from each site were uploaded to a common server and analyzed together using the same preprocessing steps. During preprocessing, images were corrected for scanner-specific gradient nonlinearity (25), registered to a common atlas space, and resampled to an isotropic 1-mm^3 spatial resolution. Further processing was performed by FreeSurfer version 5.3, and Quarc (26) was used for unbiased estimation of hippocampal volume change. The automated segmentation of FreeSurfer for hippocampal volume measurement has been shown to be comparable to results from manual tracings (27–29). Depressive symptoms were rated by the Montgomery–Åsberg Depression Rating Scale (MADRS). For sites collecting only the 17- or 24-item Hamilton Depression Rating Scale, a validated equation was used to convert the 17-item Hamilton Depression Rating Scale to a MADRS score (30).

For all modes of electrode placement used across sites, one of the electrodes was placed over the right (nondominant) hemisphere, and therefore the right hippocampus was chosen for primary analysis to determine the dose effects of repeated ECT treatments and relationships with clinical response, weighting ECT session similarly regardless of participant variations for electrode placement within or across sites. The same effects were examined for the left hippocampus, and results from these analyses are provided in the Supplement. Follow-up analyses were performed to examine the effects of BL and RUL electrode placement on both the right and left hippocampus, excluding 1 patient who received left anterior right temporal electrode placement and patients who received a combination of RUL and BL during the index series. Quality control of hippocampal segmentation was performed by procedures adapted from the Enhancing Neuro Imaging Genetics through Meta Analysis consortium (http://enigma.usc.edu/) (31).

Statistical Analysis

Statistical analysis was performed with R software (32). Slopes from linear models are reported with ± SE, and all other results are reported as mean ± SD. Primary analyses addressed relationships between 1) the number of ECT sessions and hippocampal volume change, and 2) hippocampal volume change and change in MADRS score pre- to post-ECT using the general linear model. In a subsample of patients receiving only BL or RUL ECT, the effects of electrode placement were additionally examined, and differences in slopes were tested using the function linearHypothesis in R (car-package, version 2.1-6). To control for and evaluate nonlinear effects, the number of ECT sessions squared was included as a covariate. To control for age, sex, site, baseline hippocampal volume, and baseline depression score, these variables were included as covariates in the models as specified in the Results section. Considering our a priori hypotheses and the large amount of literature showing changes in hippocampal volume with ECT (9), individual tests were considered significant at a level of $p < .01$, corresponding to a Bonferroni correction for five independent hypotheses. In the results figures, the regression lines (with 95% confidence intervals shown as shaded areas) represent the relationships between dependent and independent variables calculated without covariates. Cohen's d for volume change was calculated as mean change/SD. Finally, relationships between volume change and number of ECT sessions were additionally examined in responders (patients who had a >50% change in MADRS score over the course of ECT, $n = 150$) versus nonresponders ($n = 98$) using Welch two-sample t tests (two-sided).

RESULTS

First, we tested whether volume change of the hippocampus is positively associated with number of ECT sessions over time, including the number of ECTs squared (to estimate nonlinear effects), age, sex, site, baseline depression score, and baseline hippocampal volume as covariates. For the right hippocampus, we found that the linear component (slope) of volume change versus number of ECTs was 0.28% ± 0.083% ($t_{225} = 3.35$, $p < .001$). The square term was near significant, −0.0048% ± 0.002% ($t_{225} = -1.94$, $p = .053$), suggesting a sublinear relationship (Figure 1A), reflecting that larger volume changes occur early in the ECT treatment series. When comparing control subjects scanned at two distinct time points, no significant changes in hippocampal volume were observed (mean ± SD, 0.05% ± 0.08%, $d = 0.06$, $n = 95$, $p = .54$ [one-sample t test]). Results for the left hippocampus are presented in the Supplement and showed similarly significant volume enlargement with an increasing number of ECT sessions. Mean volumes are provided in Table 1.

Next, we tested whether clinical outcome after ECT, measured using the MADRS, is positively associated with a change in right hippocampal volume when controlling for the effects of age, sex, site, baseline depression score, and baseline hippocampal volume. Contrary to our hypothesis that patients with greater clinical response would exhibit larger volume increases, we found a negative relationship (slope, −1.0 ± 0.35, $t_{233} = -2.84$, $p < .005$) (Figure 1B), indicating less change in those with the greatest improvement. Separating patients based on the extent of clinical response over the course of ECT, volume change was 2.6% ± 2.0%, $d = 1.3$ and 3.3% ± 1.7%, $d = 1.9$ for responders (those with >50% improvement in mood scores) and nonresponders, respectively ($p = .009$) (Figure 1C). However, we also observed that the number of ECT sessions was associated with worse outcome (Figure 1D; Supplement), such that nonresponders were prescribed and received more sessions than responders (13.2 ± 4.7 vs. 11.5 ± 5.3, $t_{232.11} = 2.74$, $p = .007$). Thus, to control for differences in the length of treatment for responsive versus nonresponsive patients, the number of ECT sessions was additionally included as a covariate to the model addressing the relationship between change in hippocampal volume and change in mood rating. When additionally controlling for the number of ECT sessions, the slope of change in MADRS score versus volume change remained negative but was no longer significant (−0.69 ± 0.38, $t_{225} = -1.83$, $p = .069$). The effect size of hippocampal volume change (partial η^2) was 0.03 and 0.01 before and after adding number of ECT sessions as a covariate. As shown in the Supplement, positive relationships between left hippocampal volume enlargement and clinical change were also absent. Follow-up analyses examining the effects of ECT number and relationships with clinical outcome in ECT responders and

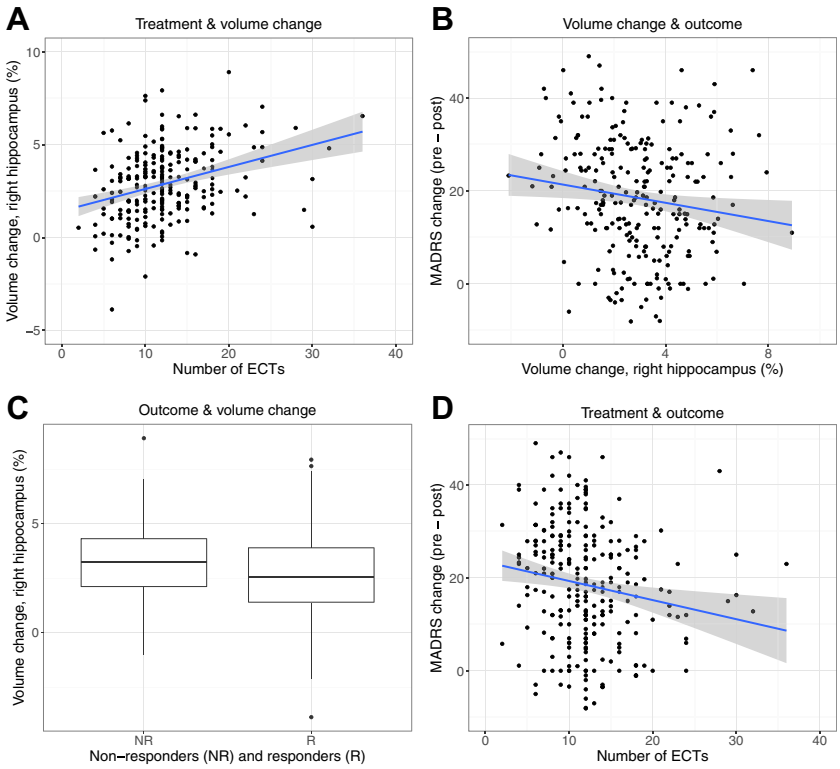

Figure 1. Differential effect of electroconvulsive therapy (ECT) on hippocampal volume and clinical outcome. **(A)** Scatter plot of volume change of the right hippocampus, computed as (posttreatment − pretreatment score)/pretreatment score × 100 vs. number of ECTs (n = 241). Slope (controlling for number of ECTs squared, age, sex, site, baseline depression score, and baseline hippocampal volume) 0.28 ± 0.08, t_{225} = 3.35, $p < .001$. **(B)** Scatter plot of change in Montgomery–Åsberg Depression Rating Scale (MADRS) score, computed as pretreatment − posttreatment score vs. volume change of the right hippocampus (n = 248). Slope (controlling for age, sex, site, baseline depression score, and baseline hippocampal volume) −1.0 ± 0.35, t_{233} = −2.84, $p < .005$. **(C)** Boxplot comparing volume change of the right hippocampus in nonresponders (NR) (MADRS reduction <50%) vs. responders (R) (MADRS reduction >50%), n = 248, $t_{234.13}$ = 2.62, p = .009. **(D)** Scatter plot of change in MADRS score vs. number of ECTs (n = 268). Slope (controlling for age, sex, and site) –0.28 ± 0.16, t_{256} = −1.80, p = .074. NRs received more ECT sessions (13.2 ± 4.7 vs 11.5 ± 5.3, $t_{232.11}$ = 2.74, p = .007) than Rs.

nonresponders for both the left and right hippocampus are presented in Supplemental Figure S1.

Finally, to investigate the effects of electrode placement, we constructed separate linear models for change in volume for the right and left hippocampus with separate slopes for the number of RUL or BL ECT sessions, controlling for age, sex, site, baseline depression score, and baseline hippocampal volume. For the right hippocampus (Figure 2A), the slopes of volume change per ECT session for RUL and BL electrode placement were both ∼0.13, suggesting similar effects for number of BL and RUL treatments. Change in volume (mean ± SD) was also similar for BL and RUL electrode placement (3.0% ± 1.7%, d = 1.8 and 2.7% ± 2.0%, d = 1.4, p = .36, t test, respectively). For the left hippocampus (Figure 2B), the slope of volume change (slope ± SE) versus number of treatments was steeper for BL (0.18 ± 0.03, $p = 1.9 \times 10^{-7}$) than RUL (0.06 ± 0.04, p = .15) electrode placements (p = .007, linear hypothesis test). The change in left hippocampal volume was also greater for BL with respect to RUL stimulation (BL 3.3% ± 2.2%, d = 1.5; RUL 1.6% ± 2.1%, d = 0.8, $p = 1.5 \times 10^{-5}$, t test). The effect of electrode placement on left hippocampal volume change was further confirmed by a number of ECTs by electrode placement interaction (p = .007) in a model of left hippocampal volume change versus the number of ECTs where electrode placement was included as a separate covariate (model 2C in the Supplement).

DISCUSSION

Including the largest sample of patients with ECT studied with neuroimaging methods to date, our findings showed a highly significant number of ECT session dose-dependent biological effect of ECT on hippocampal volume. We also showed that electrode placement differentially affects the extent of volume change in the right and left hippocampus. Specifically, BL stimulation accounts for similar changes in volume for both the right and left hippocampus, but RUL stimulation led to more focal effects in the right hippocampus. However, contrary to our expectations, we also found that volume enlargement of the hippocampus is not significantly related to treatment outcome. Instead, our results showed a negative relationship between hippocampal volume and symptom improvement, such that individuals with greater hippocampal enlargement tend to have less response. However, patients with poor response received more treatments, and this negative relationship was not significant when the number of ECT sessions were considered. This finding represents a major deviation from the common assumption in the field of a positive association between ECT-induced volume enlargement and clinical improvement. Rather, our results indicate that gross volume increase of the hippocampus by itself is not a meaningful biomarker for positive therapeutic response.

Findings from this study showed that ECT dose parameters, including the number of ECT sessions received and the location of electrode placement, modulated the magnitude and hemispheric specificity of hippocampal volume change. Here, the results demonstrated a clear and dose-dependent effect of the number of ECT sessions on hippocampal volume in both the right and left hemispheres. In addition, RUL and BL ECT showed differential effects on volume change in the left and

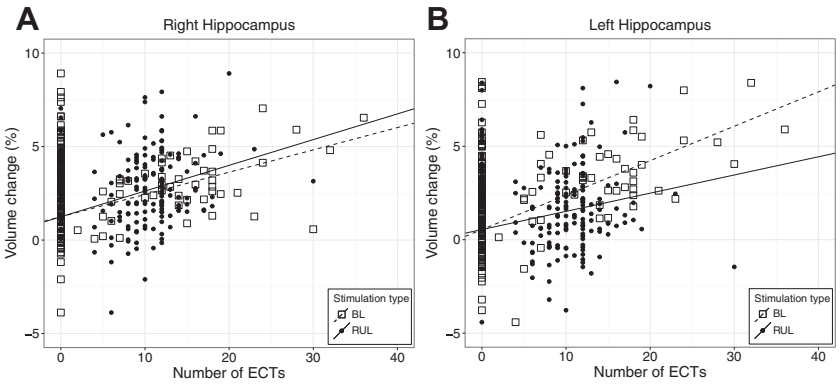

Figure 2. Effect of electrode placement on change in left and right hippocampal volume. **(A)** Changes in right hippocampal volume per number of electroconvulsive therapy (ECT) sessions for bilateral (BL, dashed line) and right unilateral (RUL, solid line) electrode placement. Both slope and change in volume was similar for BL and RUL ECT (slope of both ~0.13; BL volume increase 3.0 ± 1.7%, RUL volume increase 2.7 ± 2.0%). **(B)** Changes in left hippocampal volume per number of ECT sessions for BL (dashed line) and RUL (solid line) electrode placement. The slope was steeper and volume change greater for BL (slope 0.18 ± 0.03; volume increase 3.3 ± 2.2%) than RUL (slope 0.06 ± 0.04; volume increase 1.6 ± 2.1%) stimulation.

right hippocampus. Existing data support that the antidepressant efficacy and cognitive side effects of ECT are influenced by electrode position as well as other stimulus parameters (17,33,34). Designed to reduce cognitive side effects, electrical stimulation is focused away from the dominant (left) hemisphere with RUL electrode placement (35). In contrast, the right side of the brain is targeted by both RUL and BL electrode placements. Hence, if the electrical stimulus is modulating the volume change, a clear difference in volumetric effect of RUL versus BL stimulation for the left hippocampus is expected. In line with this hypothesis—with computational modeling results showing more prominent electric field increases in the right hemisphere for RUL ECT and in both hemispheres for BL ECT (20,21)—our results show that volume increases are greater in the right hippocampus for RUL while BL ECT leads to similar volume increases in both hemispheres (Figure 2).

Though we have shown that hippocampal volume enlargement is influenced by ECT dose parameters, the clinical relevance of these changes remains unclear. ECT-induced volume enlargement of the hippocampus (4–8) has led to the suggestion that treatment-related neuroplasticity may underlie symptom improvement (12). From a mechanistic perspective, stress in combination with genetic or epigenetic factors may reduce neurogenesis and precipitate a depressive episode, and antidepressant therapies (such as ECT) might work through restoration of the basal rate of neurogenesis in the hippocampal dentate gyrus (11). Since both left (Supplemental Figure S1B, D) and right (Figure 1) hippocampal volume changes relate to the number of ECT treatments received but do not positively associate with clinical outcome, enlargement of the hippocampus may be an epiphenomenon of ECT. The overall enlargement of hippocampal volume observed with ECT may therefore relate to seizure therapy itself rather than to the therapeutic effects of treatment.

Our results have important implications for treatment management and raise several questions and challenges relevant to understanding the neurobiological underpinnings of ECT. It is a common experience among ECT practitioners that the patients with the highest depression scores tend to be the ones with the higher response rates (36), and often these patients respond quickly. At the same time, longer depressive episodes and medication failure at baseline are indicators of poor response to ECT (37). The number of treatments prescribed is typically based on clinically determined response, and patients with modest responses are thus more likely to receive a larger number of ECT sessions in the index series (16). However, while the biological effects of ECT may be expected to relate to the number of treatments received, as shown for growth of the hippocampus, there is not an apparent parallel regarding improvement in depression score (Figure 1D).

It is conceivable that several different biological processes impact ECT clinical response; these may or may not overlap with the biological manifestations of seizure therapy itself. Animal studies support that in addition to neurogenesis, multiple other neurophysiological and neuroplastic changes occur after electroconvulsive shock (ECS). Thus, it is possible that particular microenvironmental events may influence the overall macroscopic structure of the hippocampus, while separate or concurrent processes constitute the mechanisms underlying antidepressant response. For example, changes in cellular or synaptic density and intra-/extracellular fluid might impact gross changes in hippocampal volume. Animal models have shown dose-dependent increases in markers of hippocampal neural, glial, and endothelial cell proliferation and density after ECS (15,38–40) that may result in an absolute increase in the number of synapses or specific cell types (41). Notably, a dissociation between neural changes and behavior was reported in a recent animal model study, where ECS was shown to stimulate neurogenesis but the number of new neurons did not predict the extent of behavioral outcome (42). These results are compatible with our findings with respect to the absence of clinical response relationships. At the same time, hippocampal volume may be influenced by fluid content, which may vary because of increased vascularization (43) and blood flow (44,45) or inflammation (46–48), as supported by an observed ECS upregulation of markers for microglia (49,50).

Other molecular effects that are not necessarily independent may relate more directly to antidepressant response. For example, ECS is also shown to modulate monoaminergic neurotransmission (51), similar to standard antidepressant treatment. Increased expression of brain-derived neurotrophic factor (52,53) and vascular endothelial growth factor (54) are also reported with ECS or ECT in humans and have been linked to changes in behavior (52,55). In addition, ECS elicits a

number of hippocampal epigenetic modifications, including growth arrest and DNA-damage-inducible β–dependent (GADD45B) DNA demethylation (56) and the alteration of histone and DNA modifying enzymes (57), which may influence structural neuroplasticity at both the macro and micro scales.

It is also possible that neurogenesis or other neurotrophic or neurophysiological events induced by ECT may precede or lag behind clinical response. Variations in the morphology of different regions of the hippocampus (for example, the dentate gyrus or the anterior hippocampus with more connections to neural circuits associated with mood regulation and emotional behavior) may also be more sensitive to ECT outcome. For example, analyses of change in hippocampal shape with ECT have indicated greater regional changes in the right anterior hippocampus (12) as well as changes specific to particular hippocampal subfields (7). A recent study in 24 patients also suggested that volumes of hippocampal subfields at baseline could predict response to ECT treatment (58); however, this finding needs replication in larger samples.

Our study has some limitations, most notably that the design is retrospective (e.g., no a priori standardization of magnetic resonance protocols or depression scoring) and assessments were limited to before and after treatment. In addition, the design was naturalistic, so patients who remained unresponsive were prescribed a greater number of ECT sessions on average. Other unknown moderators or speed of response, which can impact clinical decision making regarding the number of treatments prescribed (59), remain similarly unaccounted for. For example, other stimulation parameters such as pulse width and frequency and seizure threshold may also impact neural changes. However, since these parameters varied across sites, including during the ECT treatment series for individual patients, they were not investigated. Animal studies have also shown that both ECS and, to a lesser extent, chronic antidepressant treatment impact neurogenesis in the rat hippocampus (38). It is possible that the continuation of psychotropic medication during ECT might impact hippocampal structure. However, follow-up analyses revealed that the extent of volume change was similar for participants who were tapered off all antidepressants, benzodiazepines, and anticonvulsants during ECT (Supplemental Figure S2).

Cognitive side effects remain a fundamental concern in ECT practice and were not examined in this study and thus warrant future research. Future studies would also benefit from including repeated assessments at multiple time points throughout treatment to allow for examination of the trajectories and speed of change and to explore ways of subgrouping depressed individuals, possibly by identifying biological subtypes (60). Implementing machine learning approaches, with a goal of identifying individuals who are likely to respond to ECT (61), and investigations using higher-resolution imaging approaches to investigate subregions of the hippocampus (58) may also advance the field. Another avenue of future research would be studies with standardized ECT protocols across all participants to reduce confounds and increase the power of the designs to identify moderators conclusively. New approaches are needed to identify biomarkers that can explain and predict the clinical effect of ECT, separate from seizure or other procedural effects, which also may inform other antidepressant treatments.

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LO wrote the first draft and coordinated the work. LO, UK, HB, KJE, OBP, MBJ, CCA, and AMD contributed in planning and/or design the project. LO, UK, KJO, VJE, MBJ, LGH, KLN, CCA, AD, MLS, MLO, LE, MV, PS, PvE, IT, MA, RR, TH, UD, AA, and RE contributed data. LO, HB, AMD, KLN, AD, MLS, MLO, LE, MV, PS, MA, RR, AA, GH, RE, and CCA contributed in processing and/or analysis/interpretation of data. All authors contributed to manuscript revisions and approved the final version.

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