Hippocampal Volume Changes Following Electroconvulsive Therapy: A Systematic Review and Meta-analysis

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ABSTRACT
BACKGROUND: Reduced hippocampal volume is one of the most consistent morphological findings in major depressive disorder. Electroconvulsive therapy (ECT) is the most effective therapy for major depressive disorder, yet its mechanism of action remains poorly understood. Animal models show that ECT induces several neuroplastic processes, which lead to hippocampal volume increases. We conducted a meta-analysis of ECT studies in humans to investigate its effects on hippocampal volume.

METHODS: PubMed was searched for studies examining hippocampal volume before and after ECT. A random-effects model was used for meta-analysis with standardized mean difference (SMD) of the change in hippocampal volume before and after ECT as the primary outcome. Nine studies involving 174 participants were included.

RESULTS: Total hippocampal volumes increased significantly following ECT compared with pretreatment values (SMD = 1.10, 95% confidence interval [CI] 0.80–1.39, z = 7.34, p < .001, k = 9). Both right (SMD = 1.01, 95% CI 0.72–1.30, z = 6.76, p < .001, k = 7) and left (SMD = 0.87, 95% CI 0.51–1.23, z = 4.69, p < .001, k = 7) hippocampal volumes were also similarly increased significantly following ECT. We demonstrated no correlation between improvement in depression symptoms with ECT and change in total hippocampal volume (β = −1.28, 95% CI −4.51 to 1.95, z = −0.78, p = .44).

CONCLUSIONS: We demonstrate fairly consistent increases in hippocampal volume bilaterally following ECT treatment. The relationship among these volumetric changes and clinical improvement and cognitive side effects of ECT should be explored by larger multisite studies with harmonized imaging methods.

Keywords: Electroconvulsive therapy, Hippocampus, Major depressive disorder, Magnetic resonance imaging, Neuroplasticity, Volume

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Major depressive disorder (MDD) is the most common mental illness and is associated with significant morbidity and mortality worldwide (1). Persons of all ages and backgrounds suffer from MDD; furthermore, MDD has been shown to substantially impair work productivity, costing the United States approximately $210 billion per year in both direct and indirect costs in 2010 (2). Notwithstanding this tremendous toll on public health, and despite decades of research in depression, our understanding of the pathophysiology of MDD remains limited.

The neurochemical hypothesis has dominated depression research for decades and has led to important advances in the field. However, converging evidence now suggests that in addition to neurochemical changes, a variety of molecular and cellular mechanisms associated with neuroplasticity contribute to disrupted neuronal function and morphology that ultimately underlie the dysfunction of the neurocircuitry that is essential for mood regulation, cognitive function, and behavior in mood disorders. Perhaps the strongest evidence of morphological abnormalities associated with MDD is the consistent findings of reduced hippocampal volumes in MDD and other mood disorders (3). The hippocampus is one of the major structures implicated in MDD (3,4). Reduction in hippocampal volume has been seen as early as disease onset of first episode depression (5), is often exacerbated during episodes of depression compared with times of remission (6), and has been shown to correlate with memory deficits in patients with depression (7). Furthermore, reduced hippocampal volume has also been shown to correlate with the total time spent in a depressive episode in currently remitted subjects (3,8–10), suggesting an overall cumulative inhibitory effect of depression on neurogenesis.

Animal models of depression yield insights into the ways in which chronic stress may lead to volumetric reductions in the hippocampus. In rodent models, chronic stress models have been shown to lead to atrophy of hippocampal pyramidal cells (11,12), a decrease in the length and number of branch dendrites of cornu ammonis (CA) 3 pyramidal cells (13), and loss of spine synapses (14). Similarly, models of learned helplessness stress result in a decrease in synapses in CA1, CA3, and dentate gyrus layers of the hippocampus (15).
Electroconvulsive therapy (ECT) is the most effective treatment for MDD, with response rates ranging from approximately 90% in treatment-naïve patients to 50% to 70% in treatment-resistant patients (19). Despite its effectiveness and clinical use since the late 1930s, the mechanism of ECT remains poorly understood. Preclinical work has shown that electroconvulsive seizure (ECS, the animal analog of ECT) induces a number of neuroplastic processes in the hippocampus, including gliogenesis (17,18), axonal sprouting in the dentate gyrus (19), increased axospinous synapses in the CA1 pyramidal layer (20), increased number of mushroom spines (21), and neurogenesis (22,23). Furthermore, ECS has also been shown to prevent reduction in dendritic length and dendritic branch points induced by chronic stress (24). Evidence suggests that ECS induces some of these processes through the upregulation of neurotrophic factors, most notably brain-derived neurotrophic factor (BDNF), as well as vascular endothelial growth factor and basic fibroblast growth factor (25). Some evidence also suggests that angiogenesis may also be induced by ECS and may play a role in this ECS-induced increased neuroplastic activity (25); it is unclear, however, how each of these processes affected by ECS is related to the therapeutic mechanisms of ECT in humans.

Given that hippocampal volume has been shown to be reduced in patients with MDD, and that hippocampal reduction is exacerbated during depressive episodes (6), an important question is whether hippocampal volume deficits normalize following ECT, the most robust therapy for MDD. Initial imaging work in ECT was aimed at quelling the fear that ECT might produce brain damage or shrinkage in the hippocampal area (related to memory owing to the memory loss associated with ECT) in response to social stigma against the treatment (26). However, more recently several articles suggest that ECT may result in increased volume of a number of important structures, most notably the hippocampus. Given that the hippocampus is closely tied to the pathophysiology of MDD in both functional and structural imaging studies, we conducted a meta-analysis to examine whether ECT treatment for depressive disorders is associated with significant changes in hippocampal volume. We also sought to determine whether hippocampal volumetric changes correlated with clinical improvement with ECT. This correlation could be expected if the antidepressant effects of ECT were mediated through changes in plasticity in the hippocampus and if changes in plasticity were the primary contribution to volumetric changes.

METHODS AND MATERIALS

Search Strategy and Study Selection
We searched PubMed on May 31, 2016, using the following search strategy: “(ECT” or “electroconvulsive therapy”) AND (hippocamp).” We also searched the references of included studies as well as relevant reviews in the area. We included trials if they 1) examined the effects of ECT, 2) conducted volumetric brain imaging, 3) examined hippocampal volume at least at two time points (before and following a full acute course of ECT), and 4) were performed in humans.

Data Extraction
Included studies provided pre- and post-ECT volume estimates of the hippocampus. If studies reported data in a figure rather than in a table, a computer program (WebPlotDigitizer) was used to extract data points from the figures (software available at http://arohatgi.info/WebPlotDigitizer/app/). In studies where data were incomplete or could not be extracted, authors were contacted directly and asked to provide data. If individual volumetric data were not available from volumetric studies, paired t-test statistics or p values were used to estimate effect size. In addition, the average percentage improvement in each study (defined as percentage change from baseline in either the Montgomery–Åsberg Depression Rating Scale or the Hamilton Depression Rating Scale, as specified in each study), the average number of ECT sessions in each study, average age, concomitant medication status, proportion of subjects with bipolar disorder, ECT frequency and modality (unilateral vs. bitemporal), and patient status (inpatient vs. outpatient) were used.

Data Analysis and Meta-analytic Procedures
Data from the included articles were organized into an Excel spreadsheet. Our primary outcome was change in hippocampal volumes pre- and post-ECT. Statistical analysis was performed using Comprehensive Meta-analysis 3.0 (CMA 3.0; Biostat, Englewood, NJ). Our primary outcome measure for this meta-analysis was standard mean difference in reduction in hippocampal volume from pre-ECT to post-ECT. We used standardized mean difference (SMD) rather than weighted mean difference in hippocampal volume because the primary outcome measure as many studies did not provide adequate data to calculate weighted mean difference (e.g., did not report exact volumetric data but rather only a p value or t statistic from a paired t test). We report the random-effects model as our primary analysis because it is likely both more conservative and more appropriate for the data, given that ECT studies often differed slightly in the dosage, duration, and type of ECT delivered. Volumetric measurement of the hippocampus also differed in methodology between studies, and thus a random-effects model that does not assume a single underlying true effect across studies is more appropriate.

Heterogeneity between studies was evaluated using the Q statistic. This is used to provide a statistical test for significance indicating whether different effect sizes between studies are attributable to subject-level sampling error alone or to other sources of variability. Furthermore, we estimated the degree of heterogeneity using the I-squared statistic, which approximates the proportion of total variance attributable to between-study variance. Next, we assessed publication bias by plotting effect size versus standard error for each study (funnel plot). We also assessed publication bias statistically by use of the Egger’s test (27).

We conducted several stratified subgroup analyses (categorical variables) and meta-regressions (continuous variables) to examine the effects of potential moderating variables on change in volumes pre- and post-ECT. Stratified subgroup analyses were employed to examine the effects of concomitant medications, magnet strength (1.5T vs. 3T), and inpatient versus outpatient status. We conducted a test for subgroup differences using the random-effects model in CMA 3.0 to examine the association between potential moderators that were categorical variables and changes in hippocampal...
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