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Hippocampal volume changes following electroconvulsive therapy: a systematic review and meta-analysis

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Abstract

Introduction—Reduced hippocampal volume is one of the most consistent morphological findings in Major Depressive Disorder (MDD). Electroconvulsive therapy (ECT) is the most effective therapy for MDD, 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 to pre-treatment values (SMD=1.10; 95% CI 0.80–1.39; z=7.34; p<0.001; k=9). Both right (SMD=1.01; 95% CI 0.72–1.30; z=6.76; p<0.001; k=7) and left (SMD=0.87; 95% CI 0.51–1.23; z=4.69; p<0.001; 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 (beta=−1.28, 95% CI −4.51–1.95, z=−0.78, p=0.44).

Conclusion—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.

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Keywords

Electroconvulsive therapy; hippocampus; major depressive disorder; magnetic resonance imaging; neuroplasticity; volume

INTRODUCTION

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; further, MDD has been shown to substantially impair work productivity, costing the U.S. 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 the 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 neuruocircuitry that is essential for mood regulation, cognitive function, and behavior in mood disorders. Perhaps the strongest evidence of morpholoigical 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 to times of remission (6), and has been shown to correlate with memory deficits in depresses patients (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 – effects of stress on hippocampus

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 CA3 pyramidal cells (13), as well as 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 50–70% in treatment-resistant patients (16). Despite its effectiveness and clinical use since the late 1930s, the mechanism of ECT remains poorly understood. Preclinical work has shown that electroconvulsive seizures (ECS, the animal analog of ECT) induce a number of neuroplastic processes in the hippocampus, including gliogenesis (17, 18), axonal sprouting in the dentate gyrus (19), increases axo-spinous synapses in 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 neurotropic factors, most notably brain-derived neurotrophic factor (BDNF), as well as VEGF, 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 MDD patients 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 papers 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

Search Strategy and Study Selection

We searched PubMed on May 31, 2016 using the search strategy: "("ECT" or "electroconvulsive therapy") AND (hippocamp*)." We additionally 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 two time points (before and following a full, acute course of ECT) and (4) the studies were performed in humans.

Data Extraction

Included studies provided pre- and post-ECT volume estimates of the hippocampus. If studies reported in a figure rather than in a table, a computer program (Web Based Plot Digitizer) was used to extract data points from the figures (software available at http://arohatgi.info/WebPlotDigitizer/app/). In studies where data was incomplete or could not be extracted, authors were contacted directly and asked to provide data. If individual volumetric data was not available from volumetric studies – paired t-test statistics or p-values were utilized to estimate effect size. Additionally, the average percent improvement in each study (defined as percent change from baseline in either the Montgomery-Åsberg Depression Rating Scale or 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 v. bitemporal), and patient status (inpatient v. outpatient).

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; Biostat, Englewood, NJ). Our primary outcome measure for this meta-analysis was standard mean difference in reduction in hippocampal volume from pre-to-post ECT. We used standardized mean difference rather than weighted mean difference in hippocampal volume as 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 as 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 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 (1.5 Tesla v. 3 Tesla), and inpatient v. 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 volumes pre- and post-CT. The test for subgroup differences in CMA 3.0 is a chi-sq test that examines the between group heterogeneity between categories of the predictor variable. Meta-regression was utilized to examine the effects of age, gender, percent improvement in depressive symptoms, total number of ECT treatments, type of ECT administration (percent of subjects receiving right unilateral ECT), and underlying mood disorder (percent of subjects with a diagnosis of bipolar rather than unipolar depression) on the change in hippocampal volumes pre- and post-ECT. We used the random-effects model in CMA 3.0 to examine the association between each potential moderator and measured change in hippocampal volume between studies. Two studies did not report on percent of subjects with bipolar disorder and thus were not included in this meta-regression; one study recruited from both inpatients and outpatients and was thus not included in this sub-analysis (see Table S1). We had originally

planned to examine the association between change in hippocampal volumes pre- and post-ECT and response status or remission status to ECT but too few studies reported on these data to conduct this analysis.

Results

Selection of Studies

Figure 1 depicts our procedure for selection of studies. Our initial MEDLINE search yielded 313 studies, of which 285 were removed because they were reviews or commentaries, were not relevant, or were preclinical in nature. We identified 28 MRI studies examining the effects of ECT. Among these, 19 were excluded because they did not report volumetric data (i.e., functional imaging studies), were duplicate or overlapping samples, performed scans only at one time point or not following a full course of ECT, or had insufficient data (Figure 1).

Nine studies involving 174 total participants were included in this meta-analysis. The description of the studies included are reported in Table 1.

Hippocampal volume pre- and post-ECT

Total hippocampal volumes increased significantly following ECT compared to pre-treatment values (SMD=1.10; 95% CI 0.80–1.39; z=7.34; p<0.01; k=9). Figure 2 represents a forest plot of ECT's effects on overall hippocampal volume across studies. There was a moderate amount of heterogeneity between studies (Q=17.3, p=0.03, I^2=53.7%) in the fixed effects model. There was a trend suggesting publication bias using Egger's test (p=0.09). Adjusting for publication bias using Duval and Tweedie's trim and fill yielded corrected SMD for total hippocampal volumes increase of 0.97 (95% CI 0.68–1.27).

Both right (SMD=1.01; 95% CI 0.72–1.30; z=6.76; p<0.001; k=7) and left (SMD=0.87; 95% CI 0.51–1.23; z=4.69; p<0.01; k=7) hippocampal volumes were increased significantly following treatment (Figures 3, 4). Egger's tests for publication bias were not significant for right (p=0.12) or left (p=0.24) hippocampal volumes. Nonetheless, adjustments were made for publication bias and yielded corrected SMD for right and left hippocampal volumes increases of 0.93 (95% CI 0.60–1.25) and 0.77 (95% CI 0.39–1.15), respectively. There was no significant difference in the volumetric increase of right versus left hippocampus in response to ECT (SMD=0.126; 95% CI −0.173–0.425; z=0.824; p=0.41; k=7).

Moderator Analyses

In moderator analyses, there was no correlation between percent improvement in depression symptoms and change in hippocampal volume (beta=−0.35, 95% CI −3.48–2.78, z=−0.22, p=0.83). Likewise, there were no significant relationships between change in hippocampal volumes and use of concomitant medications (Q=1.75, p=0.19), magnet strength (Q=0.14, p=0.71), inpatient versus outpatient status (Q=5.12, p=0.08), age (beta=−0.0058, 95% CI −0.0382–0.0266, z=−0.35, p=0.72), gender (beta=1.39, 95% CI −0.94–3.71, z=1.17, p=0.24), percent of subjects with bipolar disorder (beta=1.26, 95% CI −0.562–3.09, z=1.36, p=0.17), mean number of ECT treatments (beta=0.063, 95% CI −0.049–0.176, z=1.10,

p=0.27), or percent of subjects receiving right unilateral ECT (beta=0.115, 95% CI −0.64–0.87, z=0.30, p=0.76).

DISCUSSION

The results of this meta-analysis demonstrate that hippocampal volumes are significantly increased bilaterally with ECT treatment. We did not, however, demonstrate any significant effects of moderating variables. This meta-analysis compiles a growing body of compelling evidence in humans that ECT directly affects structural changes in the hippocampus. These changes could potentially be explained by several processes that may be related to the treatment's mechanism of action, including, axonal and mossy fiber sprouting (19), synaptogenesis (20), gliogenesis (17, 18), neuronal maturation (21), angiogenesis (28), and neurogenesis (22, 23), all of which have been documented in animal models following ECS. While preclinical evidence suggests a specificity to hippocampal changes (i.e., genetic regulatory changes involving the upregulation of trophic support factors (29)), it is also possible that these volume changes could be explained by other non-specific processes unrelated to the mechanism of action of ECT, most notably shifts in fluid balance or a general reactive gliosis.

Relationship with Clinical Improvement

Notably, our meta-analysis did not detect a correlation between change in hippocampal volume and clinical improvement. While at least one of the included studies reported a positive correlation between hippocampal volume change and improvement in depression (30), most of the included studies' individual, patient-level regression analyses also failed to find any correlation (31–36). One additional study (not included in the meta-analysis due to significant differences in methodological approach) did find that changes in the hippocampal-amygdala complex were associated with clinical improvement in depression following ECT (37). Given the small number of included studies in the meta-analysis as well as the generally small sample sizes of the individual studies, it remains possible that our current studies are not able to detect a true effect due to small numbers of both studies and subjects. Larger scale multicenter studies that harmonize MRI methods or meta-analysis using individual patient data are needed to definitively answer the question of whether hippocampal volume change correlates with clinical improvement.

Structural Plasticity and Cognitive Impairment

Converging lines of evidence indicate that major depressive disorder and a multitude of other psychiatric disorders, are related to deficits in neuroplasticity (48). However, abrupt increases in neuroplasticity, as appears to be the case following a course of ECT, may have untoward effects other than those of alleviating psychiatric symptoms. For instance, neuroplastic changes, including hippocampal mossy fiber sprouting as well as neurogenesis, have long been documented in rodent models of epileptic disorders (49, 50). Mossy fiber sprouting in particular, has been shown to reinforce proepileptogenic neurocircuitry in animal models of epilepsy (51, 52). Furthermore, structural changes associated with epilepsy may also be related to the degree of cognitive impairments that often accompany these disorders (49). Hence, one possible unexplored consequence of changes in structural

plasticity resulting from therapeutic seizures in ECT is memory loss and other cognitive changes. Undoubtedly the most feared side effect of ECT, impairment has been seen across many cognitive domains in patients receiving ECT during the acute course (i.e., treatments 2–3 times per week). Many, though not all of these domains have consistently been shown to normalize or even exceed pre-treatment levels of cognition when measured 6 months following a course of ECT (53–55). Changes in structural plasticity may be related to these ECT-associated cognitive problems, a possibility that has not been routinely or uniformly examined in current studies. Given the importance of the hippocampus in memory formation and learning, acute neuroplastic changes (such as mossy fiber sprouting, new dendrite and synapse formation) may displace existing dendritic structure and may therefore also disrupt existing memories. Future investigations in humans should explore this possible relationship between structural plastic changes and ECT-related cognitive impairment.

Specificity of Volumetric Changes

It is possible that the volumetric hippocampal changes seen in the current study are explained by non-specific processes unrelated to the mechanism of action of ECT (i.e., inflammation, reactive gliosis, edema). However, the existing evidence suggests that ECT-related brain changes may not be fully explained by non-specific processes. A small sample of humans who underwent magnetic resonance imaging within 15 hours of ECT showed normal apparent diffusion coefficient (ADC) values in the hippocampus, suggesting no marked change in fluid shifts (56). Furthermore, the hippocampus is the most consistently reported brain area to undergo significant volumetric changes pre- and post-ECT. Other studies have variably reported changes in the amygdala (30, 36, 57), the prefrontal cortex (58), and the anterior cingulate cortex (57) following ECT. The amygdala is very proximate to the hippocampus and early imaging studies likely did not have spatial resolution to distinguish between the two structures (26). Additionally, both the prefrontal cortex and anterior cingulate cortex have been linked to depression, with network and connectivity analyses of these regions as well as the subgenual cingulate cortex offering possible predictive value of response to ECT (59, 60).

While studies did not consistently report overall brain volume changes pre- and post-ECT, at least 4 of 9 studies reported that there were no significant overall brain volume changes or hippocampal changes examined were adjusted for changes in overall brain volume (30, 31, 34, 57). Hence, it seems unlikely that hippocampal volume changes were explained by overall brain changes.

Animal models also suggest a specificity to the hippocampal region as an area where specific neuroplastic changes are taking place. ECS induces a broad range of genetic regulatory changes, many of which are involved in upregulation of trophic support factors (BDNF-MAP kinase pathway and neurogenesis gene groups); the majority of these changes occur in the hippocampus, with those changes that persist with chronic ECS almost exclusively located in the hippocampal area (29). While both neurogenesis (61) and gliogenesis (62) have been reported following ECS in the frontal cortex of rats, these and other neuroplastic changes have not been nearly as widely reported or studied in areas outside the hippocampus.

Notably, the robust hippocampal changes could be driven by low pre-treatment hippocampal volumes. Due to the heterogeneous reporting in the studies examined, it was not possible to formally examine how pre-treatment volumes moderated volume changes.

Neuroplastic changes evident following ECS

The current study strongly supports the hypothesis that ECT directly increases hippocampal volume in patients with mood disorders. There are several processes involving neuroplastic changes that may contribute to these volumetric increases. Axonal and mossy fiber sprouting (19), synaptogenesis (20), neuronal maturation (increased number of mushroom spines) (21), angiogenesis (63), gliogenesis (18), and neurogenesis (22, 23) have all been shown to be increased as a result of ECS in animal models. Although neurogenesis has been suggested to play a possible role in generating antidepressant effects (23, 64), it is likely that in terms of overall mass effect, neurogenesis would contribute substantially less than other neuroplastic processes implicated. Notably, preclinical evidence suggests that a large part of discrepant hippocampal volumes in depressed versus non-depressed animal models is explained largely by differences in neuropil and glial cell numbers, while a deficit in number of neurons may contribute a relatively small amount (65).

Potential mechanisms whereby ECS induces these processes have been shown to include upregulation of trophic support factors, most notably BDNF (66), but also vascular endothelial growth factor and neuritin (25). BDNF has been shown to protect against neurotoxicity (67) and be critical for dendritic growth and mossy fiber sprouting (68). Notably, BDNF upregulation may be necessary but not sufficient for dendritic growth and sprouting (68). Glutamatergic activation of neurons may also be necessary for these processes, as it seems to act in concert with BDNF to promote neuronal cell survival and dendritic growth in cultures (69). In humans, peripheral BDNF has been shown to increase following ECT in plasma but not serum samples (66). This discrepancy could be explained by current assay difficulties in processing human peripheral BDNF samples, which are not without significant methodological issues (70). Erythropoietin (EPO), which has potent angiogenic effects (71), may also be related to the mechanism whereby ECT/ECS induces neuroplastic changes. EPO has been shown to be upregulated in the dentate gyrus following ECS (71), which, in turn, increases BDNF in primary hippocampal neurons (72).

Clinical strategies to harness this state of increased neuroplastic changes induced by ECT may involve implementing cognitive or behavioral interventions (i.e., cognitive behavior therapy) shortly following ECT. Preliminary (75, 76) as well as more controlled (77) clinical studies have already demonstrated the potential utility of this approach. Such interventions in the acute period following ECT may be especially useful given the high relapse rates in the 6 months following ECT (78, 79) and the effectiveness of cognitive and behavioral interventions in preventing relapse in depression (80).

Limitations

Despite robust results, several limitations of this analysis require comments. First, there were relatively few studies on the topic, which limited our ability to conduct moderator analyses. We wished to conduct additional analyses examining the association of other potential

factors (e.g. remission or response status) with changes in hippocampal volume but these data was not present in the majority of studies. Second, the analysis was conducted using study-level rather than patient-level data, which further limited our ability to conduct moderator analyses. Third, due to variable reporting of results, we were only able to estimate standardized volume changes and not actual volume changes. Finally, a possibility that cannot be ruled out from the present analysis is that hippocampal volume changes may be entirely accounted for by extracellular fluid shifts or other non-specific processes and may thus be unrelated to the mechanism of action of ECT or its effects on cognitive impairment. Activity-dependent volume changes in the hippocampus have long been noted and are induced by excitatory stimulation, which is very likely occurring as a result of ECT (81). However, while excitatory stimulation may induce fluid shifts away from the extracellular space and into surrounding glia and neurons, it is not known what cumulative effect this may have on overall volume of the entire hippocampus. Lastly, because of lack of data available from previous studies, we were not able to examine ECT's effect on other brain regions, so we were not able to determine whether the brain volume changes in the hippocampus are specific to that region.

Conclusion and Future Directions

The current meta-analysis compiles a growing body of compelling evidence demonstrating that ECT directly affects hippocampal morphological changes in humans. Animal models suggest that several neuroplastic processes may contribute to this volumetric change. While we did not show that this was directly correlated with clinical improvement, our analysis was limited by a small number of studies and relatively small samples size of each study. The question of whether significant neuroplastic changes correlate with symptomatic improvement could definitively be answered by larger, multisite studies with harmonized imaging methodologies. As prior literature suggests (i.e., mossy fiber sprouting), these neuroplastic processes occur in a disorganized and haphazard fashion and may give rise to adverse effects; hence, future studies should also measure the possible correlation between morphologic changes and ECT-induced cognitive impairment. Another direction for future research would be measuring fluid balance abnormalities (diffusion-weighted imaging) pre- and post-ECT in large sample sizes. Additionally, sv2a, a new positron-emission tomography tracer which serves as a marker for synaptic density, may be useful in correlating volumetric changes with synaptogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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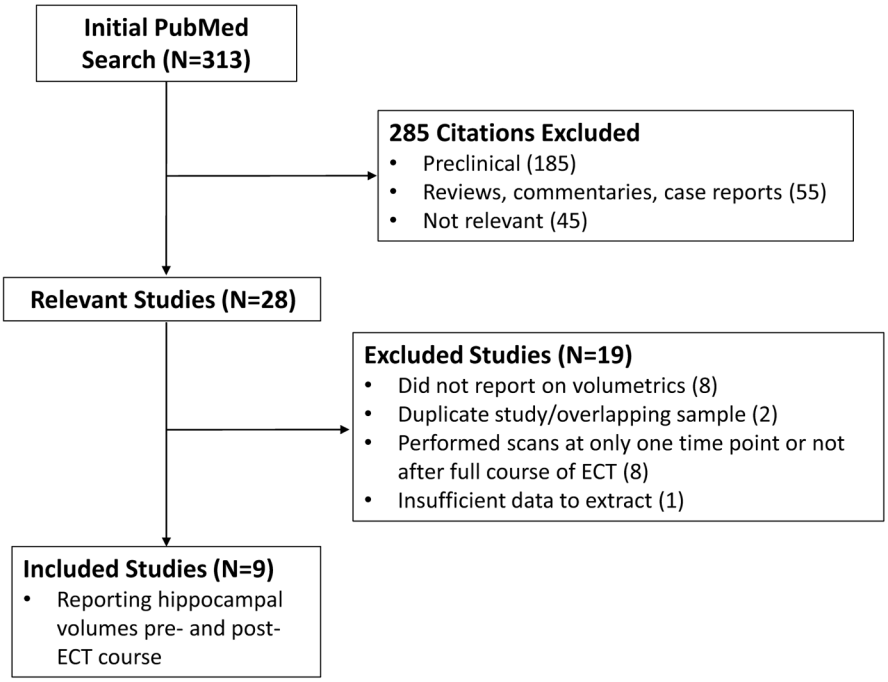

Figure 1.

Flowchart of the procedure for selection of eligible studies from identified possible references.

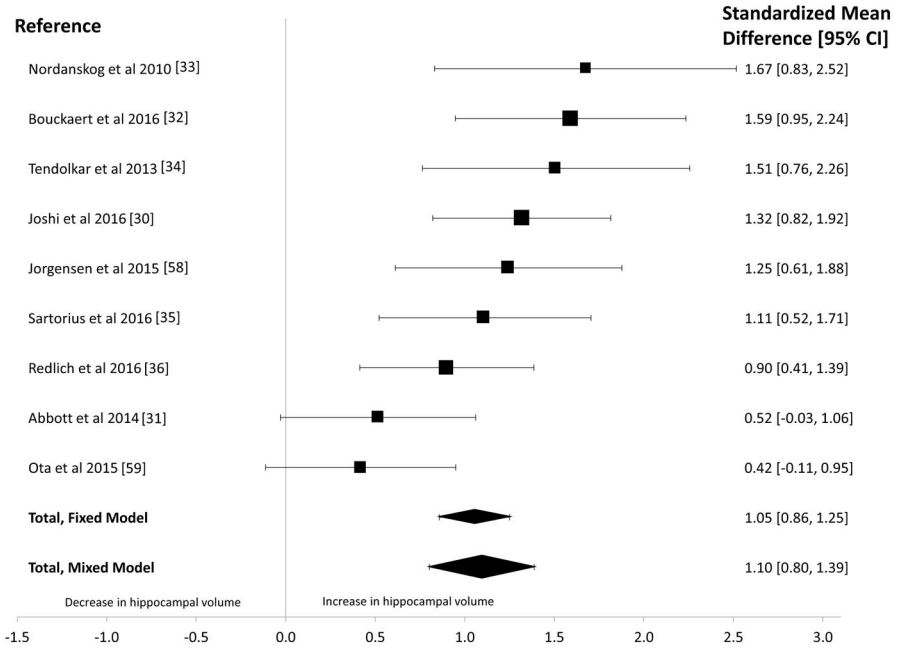

Figure 2.

Forest plot of bilateral hippocampal volumes changes following a course of ECT in mood disorders.

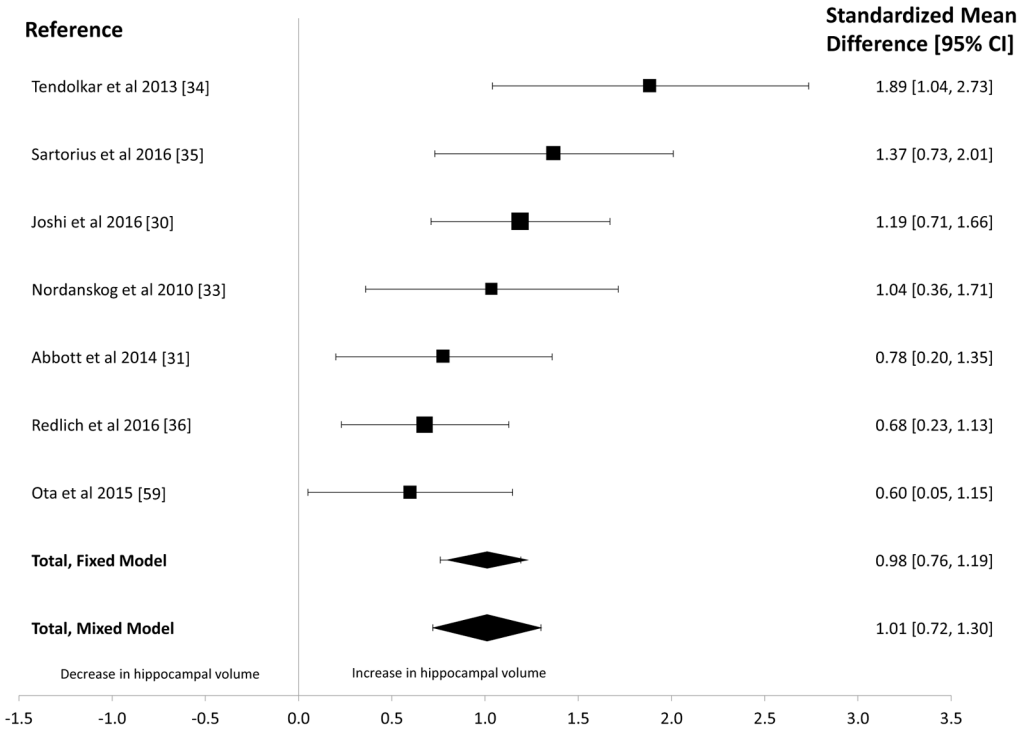

Figure 3.
Forest plot of right hippocampal volume changes following a course of ECT in mood disorders.

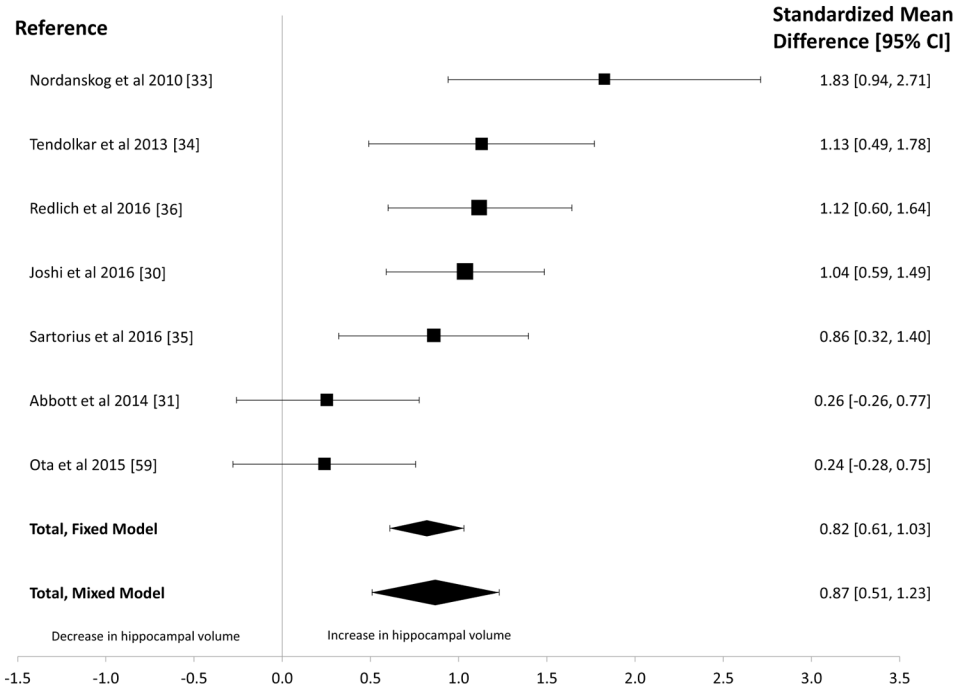

Figure 4.

Forest plot of left hippocampal volume changes following a course of ECT in mood disorders.

Table 1

Description of Included Studies

Study	N	Mean age	% Female	% Bipolar Disorder	Mean % improvement	% RUL	Medication Free	Mean no. of ECT treatments
Bouckaert et al 2016 [32]	28	71.9	71.4%	Not reported	72.6%	85.7%	No	11.2
Ota et al 2015 [59]	15	52.1	40.0%	0.0%	56.9%	0.0%	No	9.0
Jorgensen et al 2015 [58]	19	52.3	68.4%	31.6%	61.2%	0.0%	No	15.3
Joshi et al 2016 [30]	29*	42.0	53.5%	16.3%	56.0%	74.4%	Yes	11.5
Abbott et al 2014 [31]	15†	65.3	68.4%	0.0%	86.1%	89.5%	No	11.0
Nordanskog et al 2010 [33]	12	40.3	83.3%	50.0%	65.8%	83.3%	No	10.2
Tendolkar et al 2013 [34]	15	52.8	46.7%	0.0%	40.9%	0.0%	Yes	Median of 18
Sartorius et al 2016 [35]	18	52.0	50.0%	Not reported	66.7%	100.0 %	No	11.3
Redlich et al 2016 [36]	23	45.7	60.9%	0.0%	49.6%	87.0%	No	14.0

RUL indicates right unilateral; ECT, electroconvulsive therapy

*Of the full original sample, N=29 subjects were included for paired statistical tests

†Of the full original sample, N=15 subjects were included for paired statistical tests