Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis

Gbyl K, Videbech P. Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis

Objective: The main purpose of this review was to synthesise evidence on ECT’s effects on brain’s structure.

Method: A systematic literature review of longitudinal studies of depressed patients treated with ECT using magnetic resonance imaging (MRI) and meta-analysis of ECT’s effect on hippocampal volume.

Results: Thirty-two studies with 467 patients and 285 controls were included. The MRI studies did not find any evidence of ECT-related brain damage. All but one of the newer MRI volumetric studies found ECT-induced volume increases in certain brain areas, most consistently in hippocampus. Meta-analysis of effect of ECT on hippocampal volume yielded pooled effect size: $g = 0.39$ (95% CI = 0.18–0.61) for the right hippocampus and $g = 0.31$ (95% CI = 0.09–0.53) for the left. The DTI studies point to an ECT-induced increase in the integrity of white matter pathways in the frontal and temporal lobes. The results of correlations between volume increases and treatment efficacy were inconsistent.

Conclusion: The MRI studies do not support the hypothesis that ECT causes brain damage; on the contrary, the treatment induces volume increases in fronto-limbic areas. Further studies should explore the relationship between these increases and treatment effect and cognitive side effects.

Summations

- ECT-induced volume increases in both cortical and subcortical areas were consistently found in treated formerly depressed patients and a meta-analysis of the volume changes in hippocampus found an overall moderate effect size.
- Diffusion Tensor Imaging (DTI) studies point to ECT-related increases in the integrity of specific white matter tracts connecting frontal and temporal lobes.
- MRI studies did not find any evidence of brain damage after ECT.

Considerations

- Small sample size and short observation time are the main limitations in most of the studies.
- The microstructural background of the volumetric changes is unknown, and their possible association to the treatment efficacy and the cognitive side effects is not clear.
- The results of DTI studies need to be replicated due to small number of studies.
Even though ECT is the most effective treatment of severe depression (1) and has been used in clinical practice for over 70 years, several questions remain to be answered. The mechanism of action is largely unknown, although several plausible hypotheses have been proposed (2). We still do not understand why some patients relapse shortly after remission and some develop cognitive side effects and even permanent deficits in their autobiographical memory (3). These much-feared side effects in particular result in ECT being underutilised by patients and even by some doctors because of apprehension about permanent brain damage caused by the treatment (4).

Early studies of the effects of ECT on brain tissue focused on possible brain damage. Some of these found brain atrophy and enlargements of ventricles in ECT-treated patients, but were limited by several methodological issues, for example retrospective design, enrolling patients with chronic schizophrenia and using low-resolution computed tomography (5).

In the past two decades, research of ECT’s effect on the brain has shifted towards studying its mechanism of action, especially its potential to induce neuroplasticity. The pioneer MRI study investigating ECT’s effects on hippocampal volume in major depressive disorder subjects was performed by Nordanskog et al. in 2010 (6). As this group found significant increases in hippocampal volume after completing an ECT series, several other authors have corroborated their findings.

We have identified three reviews of ECT and neuroimaging, which also include structural MRI studies (7–9). However, there is need for a review that focuses only on prospective structural MRI studies and depressed patients. Such a review could increase our understanding of the underlying mechanisms of ECT’s action and hopefully reassure patients on its safety.

Aims of the study

We aimed to answer the following questions: (i) Does ECT cause volumetric changes or changes in white matter integrity and if so, what does this reflect? (ii) Do any of the changes correlate with treatment efficacy or cognitive side effects? and (iii) Is there any evidence from neuroimaging that ECT causes brain tissue damage? Furthermore, we wanted to perform an up-to-date meta-analysis of the volume changes of the hippocampus after ECT.

This systematic review adhered to the PRISMA statement (10, 11) following a predetermined protocol, which can be accessed by supporting materials (Appendix S1). PRISMA checklist can be found in Appendix S7.

The following search strategy: ‘MeSH term Electroconvulsive Therapy OR text words Electroconvulsive Therapy, Electroshock Therapy, Convulsive therapy, electric, ECT AND MeSH term Magnetic Resonance Imaging OR text words Imaging, Magnetic Resonance, NMR Imaging, Imaging, NMR, MRI scan, MRI scans, Diffusion Tensor Imaging, MRI, Structural MRI’ was used in Medline and adopted for Embase and Web of Science. English language was used as a filter. Only full-text articles (i.e. no abstracts, conference reports or other publication types) were assessed for inclusion. No restrictions regarding publication dates were imposed. The last search was conducted 31 March 2017, and limited search updates were performed until 2 December 2017.

Reference lists of included studies were scrutinised for additional papers. In several cases, authors were contacted to obtain additional information. This was especially the case in connection with the meta-analysis.

Identified records were screened by one of the authors (KG) by reading their titles and/or abstracts. The full texts of the chosen studies were retrieved and assessed for inclusion by the authors using the following eligibility criteria: (i) ECT-treated subjects aged 18+, diagnosed with either current Major Depressive Disorder or Bipolar Depression according to ICD-10 or DSM-IV; (ii) A longitudinal prospective design with at least two MRI scans, of which the first was performed just before the ECT series; (iii) Either macrostructural MRI or Diffusion Tensor Imaging (DTI) used; (iv) Macrostructural brain changes and changes in white matter integrity used as an outcome; and (v) More than five subjects.

The aim of using these restrictive criteria focusing only on a diagnosis of depression and structural MRIs was to increase the comparability between studies. The prospective design was chosen to ensure any brain pathology present before ECT was not interpreted as being caused by ECT.
If more than one study was based on an identical or overlapping sample, only the one with the highest sample was included in calculation of the overall number of participants and in the meta-analyses.

Description of data collection can be accessed through supporting materials (Appendix S2a).

Assessment of risk of bias and methodological quality

Domain-based evaluation of risk of bias in individual studies was performed systematically according to Cochrane Collaboration guidelines (12) and can be accessed through supporting materials (see Appendix S2b).

The methodology of volumetric and DTI studies was systematically assessed using a point system, and each study was assigned a quality score (QS) (Appendix S3). The criteria used for the QS were developed by the authors of this review. The QS consists of the following items: (i) number of subjects (0.1 point was assigned for every subject enrolled), (ii) the presence of control group(s) (1 point was assigned for the presence of an age- and gender-matched group of healthy controls, additional 1 point for the presence of a control group of depressed patients not treated with ECT), (iii) the number of MRI scans the control group(s) underwent (1 point assigned if the group(s) were scanned twice or more), (iv) MRI scanner field strength (1 point for 3 Tesla), (v) voxel size (1 point given for voxel size lower than 1.0 mm³; not evaluated in DTI studies due to lack of data), (vi) medication status (1 point if subjects were not medicated or if medication had been washed out in >80% of subjects before inclusion), (vii) consecutively collected sample (1 point was assigned if it was explicitly stated that a sample was collected in a consecutive way), (viii) duration of follow-up time (1 point for every MRI scan conducted later than 2 weeks after completion of the ECT series). The higher the score, the better the methodological quality.

Meta-analyses

Only studies that reported means of absolute pre- and post-ECT right and left hippocampal volumes were included (6, 13–18). In several cases, the authors were contacted to obtain the necessary information. All volumes were converted to cubic millimetres (mm³) and organised in an Excel spreadsheet. The reported volumes were not standardised to the total intracranial volume in two of the studies (6, 18). We standardised the volumes in one of them (18) applying the same method that was used by Bouckaert et al. (13) according to the formula: hippocampal volume = original hippocampal volume (OHV) – linear regression coefficient x (total intracranial volume [TIV] – mean total intracranial volume), where the coefficient was derived from a linear regression of TIV and OVH (19). We were not able to standardise volumes of the other study (6) due to lack of the necessary data. It must be noted that the remaining four studies (14–17) used slightly different methods of standardisation.

Comprehensive meta-analysis CMA 3.3 was used for statistical analysis (20). The meta-analyses were conducted by using the random-effects model weighting the studies by the inverse variance and calculating the DerSimonian-Laird effect size. The random-effects model was chosen because the included studies differ in terms of their characteristics, for example the number of ECTs in the series, electrode placements, stimulus doses, etc, and could therefore not be regarded as random samples from the same population. Furthermore, the random-effects model is more conservative. Hedges’ g was used for calculation of standardised mean differences (SMD) because it is most appropriate for studies with relative small sample sizes. To ensure the results were not skewed by a single outlier, the analyses were repeated while excluding one study at a time.

The primary outcome measure of the meta-analyses was the overall standardised mean difference (SMD) of ECT’s effects on hippocampal volume. The heterogeneity between studies was assessed by both the Cochrane Q test and I-squared statistics. Publication bias was assessed by plotting effect sizes against standard errors of the included studies (funnel plot) and also statistically, by calculation of a classic fail-safe N, which is number of missing studies that would bring P-value to > alpha.

In addition, meta-regression was conducted to examine the effects of potential moderating variables (age, percentage of females, change in depression score in rating scales, percentage of patients treated with unilateral ECT) on change in post-ECT hippocampal volume compared to pre-ECT values. The random-effects model in CMA 3.3 was used to assess the relationship between each moderator and change in hippocampal volume in the included studies.

Results

Figure 1 depicts study selection, which yielded 32 MRI studies comprising 467 patients and 285 age- and gender-matched controls. A total of 685 of 719 found records were excluded due to the...
following reasons: dual publications, diagnosis other than major depression and not describing treatment with ECT.

Older MRI studies

Five studies comprising 60 patients and five controls examined acute effects of a single ECT-session on T1 or T2 relaxation times (21–25) (Appendix S4a). Increases in these parameters are considered to reflect increased brain water content (i.e. oedema), which was hypothesised to be associated with cognitive side effects. Three lower-quality studies found T1 or T2 increases (21–23), but the two studies with the best methodology found no changes (24, 25). One of these is the study of Kunigiri et al. (25), which comprised 15 subjects, used an MRI scanner of 1.5 Tesla, and T2 measurements. They used medial temporal lobes as a region of interest (ROI), due to their putative...
ECT increases brain volume in depression

Involvement in memory, and the thalamus because evidence from animal studies shows this region is most vulnerable to breakdown of the blood–brain barrier. This study found no significant changes in T2 relaxation time 2 h after the second ECT. No correlation between changes in relaxation times and cognitive side effects were found in the two studies (22, 23) investigating this.

There are three MRI studies (n = 51 patients) that examined possible ECT-induced brain tissue damage (5, 26, 27) (Appendix S4b). The field strength of MRI scanners used ranged from 0.35 to 1.5 Tesla. The largest and best-designed is that of Coffey et al. (5), who examined 35 severely depressed patients treated with bilateral ECT. The patients were scanned at baseline before the ECT series, 2–3 days after completion of the series and at follow-up 6 months later. The post-ECT volumes of the frontal lobes, temporal lobes, hippocampus–amygdala complex, third ventricle and lateral ventricles were unchanged. Pairwise global comparison of pre- and post-ECT T1 and T2 weighted MRI scans, carried out by two blinded teams of clinicians, did not raise any suspicion of brain damage. However, a marked worsening of white matter hyper-intensities in two subjects and a possible worsening in further three subjects was present at six-month follow-up. The authors interpreted this as a progression of pre-existing cardiovascular disease, without a clear relation to ECT.

Newer volumetric studies

We included 21 studies of ECT’s effects on volume changes in the brain. These studies were based on 14 samples (6, 13, 16–18, 28–36) involving 324 patients and 268 gender- and age-matched controls (Table 1). The following 12 studies (6, 13–15, 28, 30, 36–41) were based on 5 overlapping samples comprising 94 patients and 50 controls.

Twenty of the studies found significant volume increases. One found no changes (33) and two found significant decreases (34, 35). The following paragraphs present the results of volumetric changes. The findings are divided depending on MR-data analysis approach in (i) region of interest (ROI) studies, and (ii) whole brain analysis (WBA) studies.

Region of interest. Hippocampus and amygdala. All 10 studies that measured the volume changes of the hippocampus (6, 13–18, 34, 35) and all six studies of the amygdala (14, 15, 17, 18, 34, 35), consistently reported significant post-ECT increases in their volumes compared to baseline.

Meta-analysis of hippocampal volume changes. Seven of the 10 hippocampal volume studies (n = 170 patients) were included (6, 13–18). The meta-analysis showed the right hippocampal volume increased significantly after ECT series relative to pre-ECT baseline volume (Hedges’ g = 0.39, 95% confidence interval [CI] = 0.18–0.61, z = 3.52, P = 0.000). The left hippocampal volume also increased significantly (Hedges’ g = 0.31, 95% confidence interval [CI] = 0.09–0.53, z = 2.71, P = 0.007) (Figs 2 and 3). There was no evidence that these results were skewed by a single study (an outlier). These findings correspond to an increase in volume of 4–5%.

The heterogeneity between studies was low both for the right (Q = 6.14, I² = 2.34%, P = 0.407) and left hippocampus (Q = 6.30, I² = 4.75%, P = 0.390). A visual evaluation of funnel plot for right and left hippocampus did not raise a suspicion of a publication bias. Likewise, a classic fail-safe N analysis showed the number of potentially missing studies that would make the P-value greater than alpha was 16 and 8 for the right and left hippocampal volume respectively.

In meta-regression analysis, there was a trend towards a relationship between age and change in right hippocampal volume (Z-value = −1.71; P-value = 0.086). Likewise, there was a borderline significant relationship between age and left hippocampal volume (Z-value = −1.94; P-value = 0.052). The older the age, the smaller the effect size of hippocampal volume changes. There were no significant relationships between hippocampal volume changes and the other potential moderators (gender, change in scores of depression rating scales, percentage of unilateral electrode placement) tested one at a time.

Only three studies examined hippocampal volume changes at follow-up longer than 2 weeks after completion of ECT. One study found that of 17 patients, the increased hippocampal volume was still present 4 weeks later (35), whereas two studies consisting of 10 and 23 patients found the initially increased hippocampal volume returned to baseline after 6 months without relapse of depressive symptoms (13, 38). One of these two latter studies with longest follow-up reported that 12 months after completion of ECT, the hippocampal volumes of 7 patients were without significant changes compared to baseline, while the patients were still euthymic.
Table 1. Newer volumetric MRI studies published between 2010 and 2017

<table>
<thead>
<tr>
<th>References</th>
<th>Quality score</th>
<th>Patients</th>
<th>Controls</th>
<th>MR scan time points</th>
<th>ECT RUL/BL /Mixed</th>
<th>MR data analysis approach (brain regions)</th>
<th>Regions of significant increases</th>
<th>Regions of significant decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouckaert et al. 2016 (13) *</td>
<td>10.9</td>
<td>88/79</td>
<td>0</td>
<td>T1: 1 week before T2: 1 week after T3: 6 months after</td>
<td>61/0/27</td>
<td>ROI (H)</td>
<td>H</td>
<td>None</td>
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<tr>
<td>Wade et al. 2016 (28)</td>
<td>9.3</td>
<td>53</td>
<td>33</td>
<td>T1: &lt; 24 h before T2: &lt; 24 h after 2nd ECT T3: 1 week after</td>
<td>27/1/6</td>
<td>ROI (Put, Pal, CN, NA)</td>
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<td>None</td>
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<td>Joshi et al. 2015 (14)</td>
<td>8.3</td>
<td>43</td>
<td>32</td>
<td>T1: &lt; 24 h before T2: &lt; 24 h after 2nd ECT T3: 1 week after</td>
<td>32/2/9</td>
<td>ROI (H, A)</td>
<td>H, A</td>
<td>None</td>
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<tr>
<td>Redlich et al. 2017 (29) †</td>
<td>7.3</td>
<td>23</td>
<td>21+23</td>
<td>T1: 1 week before T2: 1 week after</td>
<td>20/0/3</td>
<td>VBM</td>
<td>H</td>
<td>None</td>
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<tr>
<td>Pernia et al. 2016 (41)</td>
<td>6.9</td>
<td>29</td>
<td>29</td>
<td>T1: &lt; 24 h before T2: &lt; 24 h after 2nd ECT T3: 1 week after</td>
<td>23/0/6</td>
<td>FS, cortical thickness, ACC, STG, TP, PHG, ACC, PHC, EC, STC, ITC, FC</td>
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<td>None</td>
</tr>
<tr>
<td>Van Eijndhoven et al. 2016 (30)</td>
<td>5.3</td>
<td>23</td>
<td>22</td>
<td>T1: 1 week before T2: &lt; 1 week after</td>
<td>0/19/0</td>
<td>FS, cortical thickness</td>
<td>TC, I</td>
<td>None</td>
</tr>
<tr>
<td>Cano et al. 2017 (31)</td>
<td>5.2</td>
<td>12</td>
<td>10</td>
<td>T1: &lt; 48 h before T2: &lt; 48 h after 1st ECT T3: &lt; 48 h after 9th ECT T4: 2 weeks after</td>
<td>0/12/0</td>
<td>VBM</td>
<td>H, A, PgACC,</td>
<td>None</td>
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<td>Qiu et al. 2016 (32)</td>
<td>5.2</td>
<td>12</td>
<td>15</td>
<td>T1: 1 day before T2: after 8th ECT</td>
<td>0/12/0</td>
<td>VBM</td>
<td>H, A</td>
<td>None</td>
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<td>Nickl-Jockschat et al. 2016 (33)</td>
<td>5.1</td>
<td>21</td>
<td>22</td>
<td>T1: before T2: 2-16 days after</td>
<td>9/0/12/0</td>
<td>VBM</td>
<td>No changes</td>
<td>None</td>
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<td>Dukart et al. 2014 (34) ‡</td>
<td>5.0</td>
<td>10</td>
<td>21+24</td>
<td>T1: baseline T2: 3 months after baseline T3: 6 months after baseline</td>
<td>10/0/0</td>
<td>VBM</td>
<td>H, A, ATL, I, SC, H, A, ATL, SC,</td>
<td>PFC (only compared to non-ECT controls)</td>
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<td>Bouckaert et al. 2015 (37)</td>
<td>4.8</td>
<td>28</td>
<td>0</td>
<td>T1: 1 week before T2: 1 week after</td>
<td>24/0/4</td>
<td>VBM</td>
<td>MTL, CN, I, PSCT</td>
<td>None</td>
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<td>Nordanskog et al. 2010 (6)</td>
<td>2.2</td>
<td>12</td>
<td>0</td>
<td>T1: &lt; 1 week before T2: &lt; 1 week after</td>
<td>10/0/2</td>
<td>ROI (H)</td>
<td>H</td>
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<tr>
<td>Nordanskog et al. 2014 (38)</td>
<td>4.0</td>
<td>10</td>
<td>0</td>
<td>T3: 6 months after T4: 12 months after</td>
<td>10/0/2</td>
<td>ROI (H)</td>
<td>H returned to baseline values</td>
<td>None</td>
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<td>References</td>
<td>Quality score</td>
<td>Patients</td>
<td>Controls</td>
<td>MR scan time points</td>
<td>ECT RUL/BL/Mixed</td>
<td>MR data analysis approach (brain regions)</td>
<td>Regions of significant increases</td>
<td>Regions of significant decreases</td>
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<tr>
<td>Jørgensen et al. 2016 (35)</td>
<td>3.9</td>
<td>19</td>
<td>0</td>
<td>T1: before</td>
<td>0/16/3</td>
<td>ROI (H, A, T, PFC, DLPFC)</td>
<td>H, A, T</td>
<td>DLPFC (T2 vs T1, not present at T3)</td>
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<td>T2: 1 week after</td>
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<td></td>
<td></td>
<td></td>
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<td>T3: 4 weeks after</td>
<td></td>
<td></td>
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<tr>
<td>Sartorius et al. 2016 (17) §</td>
<td>3.8</td>
<td>18</td>
<td>36</td>
<td>T1: 1-2 days before</td>
<td>NK</td>
<td>VBM</td>
<td>TL, PH, I, FG</td>
<td>None</td>
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<td>T2: &gt; 2 days &lt; 2</td>
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<td></td>
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<td></td>
<td></td>
<td>weeks after</td>
<td></td>
<td>ROI (H, A, habenula)</td>
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<tr>
<td>Abbott et al. 2014 (16) ¶</td>
<td>3.5</td>
<td>19/15</td>
<td>20</td>
<td>T1: &lt; 2 days before</td>
<td>17/20</td>
<td>ROI (H)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T2: &gt; 5 days after</td>
<td></td>
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<tr>
<td>Depping et al. 2017 (36)</td>
<td>3.2</td>
<td>12</td>
<td>21</td>
<td>T1: 5 days before</td>
<td>12/0/0</td>
<td>VBM</td>
<td>parts of cerebellum</td>
<td>None</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>T2: 6-8 days after</td>
<td></td>
<td>ROI (cerebellum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomann et al. 2017 (39) **</td>
<td>3.2</td>
<td>12</td>
<td>21</td>
<td>T1: 5 days before</td>
<td>12/0/0</td>
<td>VBM</td>
<td>MTL</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
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<td>T2: 6-8 days after</td>
<td></td>
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<tr>
<td>Wolf et al. 2016 (40) **</td>
<td>3.2</td>
<td>12</td>
<td>21</td>
<td>T1: 5 days before</td>
<td>12/0/0</td>
<td>VBM, SBM</td>
<td>MTL network</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2: 6-8 days after</td>
<td></td>
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<tr>
<td>Tendolkar et al. 2014 (15)</td>
<td>2.5</td>
<td>15</td>
<td>0</td>
<td>T1: &lt; 1 week before</td>
<td>0/12/0</td>
<td>ROI (H, A, SBV)</td>
<td>H, A</td>
<td>None</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T2: &lt; 1 week after</td>
<td></td>
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<tr>
<td>Ota et al. 2015 (18)</td>
<td>1.5</td>
<td>15</td>
<td>0</td>
<td>T1: before</td>
<td>0/15/0</td>
<td>VBM</td>
<td>H, PH, ITC, SgACC</td>
<td>None</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T2: after</td>
<td></td>
<td>ROI (H, A, ACC)</td>
<td>H, A</td>
<td></td>
</tr>
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</table>

Symbols:
* 79 out of 88 patients underwent the first MRI scanning;
† two control groups (healthy controls and non-ECT patients, i.e. depressed patients treated only with medication);
§ the design differs from other studies, for details see the full text;
¶ MR-data of the control group were obtained from a register;
‖ MR-data only of 15 responders analyzed;
** the results presented in the table apply only to patients diagnosed with major depression;
# RALT - right anterior left temporal (some patients switched to RALT electrode placement);

Abbreviations:
ECT, electroconvulsive therapy; before, before start of ECT series; after, after the end of ECT series; h, hours; MR, magnetic resonance; RUL, right unilateral; BL, bilateral electrode placement; ROI, region of interest; NK, not known; VBM, voxel-based morphometry; VBCT, voxel-based cortical thickness; SBM, source-based morphometry; FS, Free Surfer;

Brain regions:
SBV, supratentorial brain volume; H, hippocampus; A, amygdala; T, thalamus; TL, temporal lobe; TP, temporal pole; TC, temporal cortex; ATR, anterior temporal pole; ATL, anterior temporal lobe; SC, subgenual cortex; I, insula; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; MTL, medial temporal lobe; PSTC, posterior superior temporal cortex; Put, putamen; Pal, pallidum; CN, caudate nucleus; NA, nucleus accumbens; ITC, inferior temporal cortex; ACC, anterior cingulate cortex; SgACC, subgenual anterior cingulate cortex; PACC, perigenual ACC; PH, parahippocampus; PHG, parahippocampal gyrus; PHC, parahippocampal cortex; STG, superior temporal gyrus; STC, superior temporal cortex; EC, entorninal cortex; FC, fusiform cortex;
Other ROIs. The anterior cingulate cortex (ACC) was ROI in three studies (18, 34, 41). The first two found significant ECT-induced volume increases.

The prefrontal cortex (PFC) was measured in two studies (34, 35). Dukart et al. found grey matter volume (GMV) decreases in the right middle and inferior frontal cortex, as well as in the frontal premotor cortex of patients who were treated with ECT. However, the decreases were only present in comparison with depressed patients receiving medication only, not compared to healthy controls (34). Moreover, the depressed patients treated solely with medication showed a larger GMV, which is possibly disease-related, in the same areas of the PFC compared to healthy controls. Jørgensen et al. found GMV decreases in the dorsolateral PFC in patients right after completion of ECT compared to baseline, but not at follow-up 4 weeks later (35).

Thalamus (35), the left putamen of the four examined striatal nuclei (28) and the affective/limbic part of cerebellum (36), was the other ROIs, in which significant volume increases were found after ECT.

Whole brain analysis. Of the 13 studies applying the WBA approach, 10 used voxel-based morphometry (VBM) to measure grey matter volume (GMV) and three used either Free Surfer (FS) or voxel-based cortical thickness (VBCT) to measure cortical thickness changes.

All but one (33) of the studies that measured GMV found increases in patients after completion of a ECT series compared to baseline. The increases were reported most consistently in the medial temporal lobe, including the hippocampus, amygdala and parahippocampus. Other less reported areas were the insula, other parts of the temporal lobe (temporal pole, superior and inferior...
temporal gyrus), parts of the anterior cingulate cortex (ACC), and the caudate nucleus. For details and references, see Table 1.

All three studies measuring changes in the cortical thickness found significant increases in patients after the end of the ECT series compared to baseline, and no decreases were found. The increases were most consistently reported in the temporal lobe – including the temporal pole, the superior, middle, inferior and parahippocampal gyrus – in the insula and in the ACC (17, 30, 41).

Diffusion tensor imaging studies

Five DTI studies comprising 92 patients and 62 healthy controls are presented in Table 2 (33, 35, 42–44). All but one (33) found significant ECT-induced changes in different DTI parameters, that is increases in fractional anisotropy (FA) and decreases in radial diffusivity (RD) and mean diffusivity (MD) in white matter (WM) of the frontal and temporal lobes. These changes indicate increased WM integrity (i.e. increased structural connectivity).

The most methodologically sound study found the above-mentioned changes bilaterally in the anterior cingulum, forceps minor and in the left superior longitudinal fasciculus (SLF) in 20 depressed patients after completion of ECT series compared to baseline (42). No significant changes were present in the healthy controls over time.

Relationship between volume and clinical effects

Of the 21 volumetric studies, 18 analysed the relationship between volumetric changes and clinical improvement. Only seven of them found such a

<table>
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<th>Table 2. Diffusion tensor imaging (DTI) studies</th>
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<tr>
<td><strong>Reference</strong></td>
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<tr>
<td>Lyden et al. 2014 (42)</td>
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<td>Nickl-Jockschat et al. 2016 (33)</td>
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<td>Jørgensen et al. 2016 (35)</td>
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<td>Zeng et al. 2015 (43)</td>
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<td>Nobuhara et al. 2004 (44)</td>
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Symbols:
†: increase; ↓: decrease; #: RALT - right anterior left temporal (some patients switched to RALT electrode placement);

Abbreviations:
ECT, electroconvulsive therapy; before, before start of a ECT series; after, after the end of a ECT series; h, hours; MR, magnetic resonance; RUL, right unilateral; BI, bilateral electrode placement; WBA, whole brain analysis; ROI, region of interests; TBSS, tract-based spatial statistics; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; AC, anterior cingulate; FM, forceps minor; SLF, superior longitudinal fasciculus; ATR, anterior thalamic radiation; OCC, occipital cortex;
relationship (see Appendix S5). In the different studies, such a relationship was found in diverging regions. Only few of these seven studies reported the assessment of this relationship as a primary outcome. Two of five DTI studies found a relationship between increased WM integrity and clinical improvement (42, 43).

None of the studies that examined the relationship between volumetric changes and cognitive tests found any association (16, 36–38). The two older MRI relaxometry studies, which conducted correlational analyses, did not find a relationship between T1 and T2 relaxation times increases and cognitive side effects (22, 23).

Only a few authors found baseline (pre-ECT) volumetric measurements predicted treatment effects. Smaller baseline hippocampal – but not amygdalar – volumes and smaller baseline hippocampal, amygdalar and subgenual ACC volumes predicted treatment response in the studies of Joshi et al. (14) and Dukart et al. (34) respectively. One study suggested an entire set of shape and volume morphometry data (i.e. measurement of both volumes and shapes of specific brain structures) could predict treatment response with up to 89% accuracy (28).

Risk of bias

Generally, regarding the evaluated domains, there was a low risk of bias in the older studies (Appendix S6b). The newer studies were characterised by high risk of confounding bias, which was evident in 58.3% of them due to the concomitant psychotropic medication during the ECT-series. A high risk of attrition bias was present in 20.8% of the studies due to drop out at follow-up. Selective outcome reporting and detection risk of bias were evaluated as low in nearly all of the studies (Appendix S6a).

Discussion

Older studies

Neither older (published 1987–2007) MRI studies using ROI methods nor newer ones using VBM found any evidence of ECT-induced brain damage. Furthermore, three newer studies of cortical thickness found no reductions after ECT (17, 30, 41).

This is in line with a comprehensive review combining data from neuroimaging, quantitative cell counting, autopsy of deceased ECT patients, animals treated with electroconvulsive seizures (ECS) and studies of patients with epilepsy (45). This is also in agreement with a study that used diffusion weighted imaging (DWI), which is considered to be very sensitive in detecting any early or small focal tissue changes. This study did not find any changes after ECT (46). Furthermore, no increases in brain damage markers were found in the plasma of depressed patients after a course of ECT in four of the five studies that measured glial cell protein S100b and all studies that measured neuronal-specific enolase (NSE) (47–49).

This lack of evidence of ECT-associated brain tissue damage, even when using state-of-the-art MRI, corroborate the findings of other recent systematic reviews on mortality rate (50) and safety of ECT (51). The former found the ECT-related mortality rate to be 2.1 per 100,000 treatments, which was lower than the mortality rate associated with general anaesthesia in relation to surgery (3.4 per 100,000). The latter found that maintenance-ECT among elderly patients with depression was well tolerated, although this group is in higher risk of neurological and cardiovascular complications compared to younger patients. In accordance a Danish register-based cohort study of all psychiatric in-patients admitted to a psychiatric hospital in the course of 25 years found overall mortality rate from natural causes were lower among ECT-receivers than those patients who were not treated with ECT (RR = 0.82) (52).

Newer volumetric and DTI studies

Newer MRI studies (published 2010–2017) revealed ECT-induced volumetric increases in cortical and subcortical brain areas, most consistently in the hippocampus. Hippocampal volume increase was already present after a few ECT sessions and increased to its maximum after the end of the ECT series. It then returned to baseline at the 6-month follow-up. Our meta-analysis of ECT’s effects on hippocampal volume found a moderate effect size both for the right and left hippocampus and meta-regression found borderline significant negative association between age and the left hippocampal volume change. Compared to our results, a recent meta-analysis found substantially higher effect sizes and no association between age and volume changes (53). These discrepancies may be due to the fact that this group had not included the largest study in the field, namely the work of Bouckaert et al. comprising of elderly patients (13). Another reason for this difference might be that we, in contrast to Wilkinson et al., meta-analysed only the studies that were able to provide actual hippocampal volumes. Furthermore, a very recent meta-analytic study
corroborated the results of our meta-analyses reporting slightly greater, but still moderate effect sizes (54). Moreover, the negative association between age and left hippocampal volume change reached level of significance in their meta-regression analysis (54). This may be explained by the fact that they included one study that was excluded from our meta-analysis due to the lack of actual hippocampal volumes. In addition, Takamiya et al. expanded results of our meta-analyses by finding a negative association between percentage of responding and remitting patients and hippocampal volume changes. They also meta-analysed amygdalar volume changes and found increases with moderate effect sizes bilaterally.

DTI studies point to an ECT-induced increase in FA and a concurrent decrease in MD and RD of the WM pathways in the frontal and temporal lobes, which indicates an increased integrity of these tracts (42, 55).

The question is whether these volume increases and the increase in WM integrity reflect neuroplasticity processes central to the mechanism of ECT action, or if they are an epiphenomenon, e.g. an unspecific tissue reaction to electric current or seizures, such as reactive gliosis or neuroinflammation.

Neuroplasticity

It is interesting that the ECT-induced structural changes are not widespread in the brain but localised in the areas overlapping those considered to be central to the pathogenesis of major depression.

Hippocampal function has most notably been linked to depression in several studies (56, 57). Furthermore, smaller hippocampal volume has been linked to major depression in meta-analyses (58, 59) and treatment of depression with antidepressants (60, 61), vagus nerve stimulation (VNS) (62) or repetitive transcranial magnetic stimulation (rTMS) (63) has been shown to increase the volume of this structure. An 11-year follow-up study of formerly depressed patients showed the initial hippocampal atrophy apparently disappeared in the euthymic patients 11 years later (64).

A recent meta-analysis reported thinner grey matter in several cortical areas in a huge sample of depressed patients (65), especially in those areas shown to increase in size after ECT in this review. Likewise, a decreased integrity of specific WM pathways has been reported (66–68), namely in the left superior longitudinal fasciculus and the anterior thalamic radiation, and these pathways clearly overlap with those in which an ECT-induced increase in integrity has been found in this review.

Moreover, there is a solid body of evidence that electroconvulsive seizures (ECT), an animal model of ECT, induces neurogenesis (69, 70) and synaptogenesis in the rat hippocampus (71), as well as angiogenesis and gliogenesis in the rat frontal cortex (72). Likewise, studies of ECS in nonhuman primates have shown glio-, angio- and neurogenesis (73).

Furthermore, meta-analyses of depressed patients have shown decreased levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) compared to healthy controls. ECS upregulates the BDNF mRNA and protein expression in animal brains (74, 75) and ECT increases the plasma, but not serum or full blood level of BDNF in patients with depression (13, 35, 75, 76). However, these changes of BDNF level do not seem to be related to treatment effects (13, 35, 75, 76).

Besides, three studies using hydrogen-1 magnetic resonance spectroscopy found an increase of choline-containing compounds (an indirect indicator of neuroplasticity) in the hippocampus of depressed patients after ECT treatment (35, 77, 78). In addition, dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis with a subsequent hypercortisolemia-related suppression in neuroplasticity has been found in a substantial number of depressed patients (79, 80).

Finally, our meta-regression analysis found a trend towards a significant relationship between age and size of the ECT effects on hippocampal volume (i.e. the higher the age, the smaller the effect size of volume changes). Although speculative, this could reflect the processes of neuroplasticity are slower in aging mammalian brains (81, 82).

Therefore, an important effect of ECT might be the upregulation of neurotrophic factors promoting neuroplasticity processes that reorganise depression-related neuronal circuits. In late-onset depression, which is believed to be linked to an increased density of white matter lesions (WMLs) located in the specific pathways crucial for emotional regulation and cognition (68, 83), ECT could lead to improvements in WM integrity through its neuroplasticity effects. However, these hypotheses, in particular the latter, are still rather speculative.

Oedema does not seem to be a plausible explanation of the volumetric increases, as no evidence of ECT-associated oedema was found using a variety of techniques, such as T2 relaxometry (25), DWI (46), FLAIR (6) and DTI (35).
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Correlation between structural changes and clinical effects

Most studies in this review did not find any correlation between structural changes and the effects of treatment.

However, this lack of correlation may be explained by small sample sizes. In addition, in a few studies with a six- and twelve-month follow-up, a favourable treatment effect persisted, although the hippocampal volume returned to baseline. This does not favour a hypothesis that hippocampal volume increases are necessary for treatment response and the sustained remission.

All four studies that tested the relationship between volumetric changes and cognitive side effects did not find such an association. Analogously to the discussed relationship with clinical improvement, the studies might be underpowered. Furthermore, none of these studies measured autobiographical memory deficits, the type of cognitive side effect, which ECT-treated patients often complain about (3). One study used Mini Mental State Examination (MMSE) to assess ECT-related cognitive side effects. The MMSE gives a crude measure of cognition (84) and is therefore unsuitable for a reliable assessment of ECT-related side effects (85).

The processes related to hippocampal volume increase may be linked to cognitive side effects. Firstly, volumetric changes are found most consistently in the hippocampus, which plays a key role in memory formation. Secondly, both ECT-related cognitive impairment and hippocampal volume increases are transient and most pronounced after the completion of an ECT series. Lastly, a DTI study found an FA decrease (suggesting decrease in the integrity of the tissue) in the hippocampus after ECT treatment. Therefore, it is tempting to speculate that the transient cognitive impairment may be linked to a dynamic reorganisation of the hippocampal tissue triggered by ECT. In contrast to physiological neuroplasticity-inducing stimuli like learning and physical activity, a non-physiological stimulus like seizure is much stronger, which potentially may give rise to greater neuroplasticity effects. However, one study did not find any significant correlation between reversal of memory impairment and return of hippocampal volume to baseline value (38).

Strengths and limitations

The key strength of this review is that strict criteria were used in terms of study selection, with focus only on prospective studies investigating patients with depression and using structural MRI.

The limitations of the included studies must be acknowledged. The older studies used scanners with low field strength (0.08–1.5 Tesla), resulting in low resolution and low signal-to-noise ratio. Also, these studies conducted rather crude volumetric measurements made by a human observer. The newer studies used higher field strength scanners (mainly 3 Tesla) and computerised, reproducible methods of MRI data analysis, but they also have some limitations. Firstly, nearly all studies have a small sample size (n = 10–66), which increases the risk of type-II errors. Secondly, most of the studies lack long-term follow-up and the few studies with longer follow-up suffer from a substantial attrition rate. Thirdly, some studies lack a control group or apply a control group that is scanned only at baseline; thus, they are unable to control for any changes in the controls between the two different time points. Fourthly, many newer studies allow concomitant psychotropic medication giving rise to confounding, which might exaggerate the magnitude of volume increases. Finally, no study applied a control group of untreated depressed patients. However, this would be very difficult due to ethical reasons.

There are also several limitations at the review level. First of all, we did not included studies published in languages other than English as well as those reported as abstracts or conference reports, which might be the source of publication bias. In particular, non-publication of negative results could invalidate our meta-analysis. However, the assessment of the fail-safe N showed a low risk of that type of bias. Secondly, the criteria used for assessment of methodological quality of the included studies were developed for this review. Therefore, although intuitive, it is not yet an established and validated method. Thirdly, the hippocampal volumes of one of the studies included in our meta-analysis were not standardised and some of the other studies used slightly different methods of standardisation. However, it is unlikely that this would change the result of our meta-analyses. An analysis (not shown) proved that if the volumes were not normalised to total brain volume it would introduce noise and subsequently higher SDs, whereas the mean changes in volumes would be unaltered. Lower effect sizes would therefore be the net result of no normalisation. Furthermore, exclusion of each of the studies one at a time did not alter the final result. Finally, some volumetric studies were based on identical or overlapping samples of patients. We have dealt with this by including only the paper with highest number of patients in
the calculation of the overall sample size of the volumetric studies. However, all these studies were mentioned in the qualitative analysis because they contributed with different results based on different analyses.

To sum up, the prospective MRI studies investigating the adverse effects of ECT on brain structure did not find any evidence of brain damage. On the contrary, newer MRI studies consistently found ECT-induced volume increases in different brain areas considered to be involved in emotional regulation. These increases do not seem to be caused by oedema. Instead this may be related to neuroplasticity, but it has not been proved yet. The results of the correlation of these increases to treatment efficacy are inconsistent, and their relation to cognitive side effects has not been sufficiently investigated. The DTI studies point to ECT-induced increases in the integrity of WM pathways within the frontal and temporal lobes, but the results need to be replicated due to the small number of studies.

The problem of the small sample size of ECT studies may hopefully be addressed by initiatives like the Global ECT-MRI Research Collaboration (GEMRIC) (86). Future investigations with larger sample sizes need to establish the correlation between volumetric increases and treatment effects and cognitive side effects and need also to use the same neuropsychological test battery to facilitate future meta-analyses of this relationship. Neuropathological autopsy studies could provide direct insight into the neuronal cytoarchitecture of these increases. Some indirect insight could be achieved by multimodal MRI (anatomical, DWI, DTI, MR spectroscopy, resting state functional MRI or cerebral blood flow sequences) used in the same sample of patients.

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**Declaration of interests**

Both authors have nothing to declare.

**References**


ECT increases brain volume in depression


Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Study protocol.

Appendix S2. Description of data collection (2a) and assessment of risk of bias (2b).

Appendix S3. Assessment of the methodological quality of the volumetric and DTI studies.
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**Appendix S4.** Older MR T-relaxometry studies of acute effects of a single ECT on T1 and T2 relaxation times (4a) and Older MRI studies of effects of ECT on brain structure 4(b).

**Appendix S5.** Studies that found significant relationship between the clinical improvement and increases of brain volumes.

**Appendix S6.** Assessment of risk of bias in newer volumetric studies including DTI studies (6a) and Assessment of risk of bias in older studies (6b).

**Appendix S7.** PRISMA 2009 checklist.