Hippocampal volume in relation to clinical and cognitive outcome after electroconvulsive therapy in depression

Nordanskog P, Larsson MR, Larsson E-M, Johanson A. Hippocampal volume in relation to clinical and cognitive outcome after electroconvulsive therapy in depression.

Objective: In a previous magnetic resonance imaging (MRI) study, we found a significant increase in hippocampal volume immediately after electroconvulsive therapy (ECT) in patients with depression. The aim of this study was to evaluate hippocampal volume up to 1 year after ECT and investigate its possible relation to clinical and cognitive outcome.

Method: Clinical and cognitive outcome in 12 in-patients with depression receiving antidepressive pharmacological treatment referred for ECT were investigated with the Montgomery–Asberg Depression Rating Scale (MADRS) and a broad neuropsychological test battery within 1 week before and after ECT. The assessments were repeated 6 and 12 months after baseline in 10 and seven of these patients, respectively. Hippocampal volumes were measured on all four occasions with 3 Tesla MRI.

Results: Hippocampal volume returned to baseline during the follow-up period of 6 months. Neither the significant antidepressant effect nor the significant transient decrease in executive and verbal episodic memory tests after ECT could be related to changes in hippocampal volume. No persistent cognitive side effects were observed 1 year after ECT.

Conclusion: The immediate increase in hippocampal volume after ECT is reversible and is not related to clinical or cognitive outcome.

Significant outcomes

- The immediate increase in hippocampal volume seen in patients with depression treated with electroconvulsive therapy (ECT) returned to baseline levels after 6 months.
- There was no significant correlation between the changes in hippocampal volume and clinical or cognitive outcome, but a positive correlation was found between the immediate increase in left hippocampus and the number of treatments.
- No persistent cognitive side effects were seen 1 year after ECT.

Limitations

- Our findings should be interpreted with caution due to the small sample size and statistical limitations. Further studies with larger samples are needed to investigate the generalizability of these findings.
- Random bias cannot be excluded in an observational study such as this.
- Magnetic resonance imaging lacks the ability to characterize the different internal components constituting hippocampal volume.
Introduction

The biological model currently used to conceptualize the nature and course of depression involves structural changes in the hippocampus (1–3). Reduced plasticity of the hippocampus has been found to be correlated to stress and depression in both preclinical animal models and human post-mortem studies (4, 5). It has also been concluded from clinical structural imaging studies that patients with depression have a smaller hippocampal volume than healthy subjects (6, 7) and that hippocampal volume reduction is related to the course of depressive illness (8–10). Reductions in size have also been found in cerebral structures other than the hippocampus in patients suffering from depression, especially the frontal regions (11, 12). In a recent study, Järnum et al. (12) also found that non-responders to antidepressive treatment had a thinner cortex in the posterior cingulate at baseline than those who responded to treatment. A lower hippocampal volume at baseline has also been shown to predict poorer response to treatment (13).

An important question is to what extent these structural changes should be interpreted as trait-dependent, predicting vulnerability to depression, or state-dependent, and thus an important target for treatment. Preclinical studies have established that the activation of processes leading to increased plasticity of the hippocampus is part of the mechanism of action of antidepressive treatment (14–19), suggesting a possible state-dependent counteracting mechanism at a structural level. Corresponding clinical findings of hippocampal volume changes together with antidepressive treatment and response rate are still inconclusive. A treatment-related increase in volume of the hippocampus has been reported in a few clinical studies (20–23), but without any relation to response rate. Other studies have failed to find an association between hippocampal changes and antidepressive treatment (24). The extent to which structural changes in the hippocampus is a clinically important target for the treatment of depression remains elusive (25, 26).

Electroconvulsive therapy (ECT) is the most effective means of treating severe depression (27), and it has been suggested that its superior antidepressive effect is related to its powerful effect on cell proliferation in the hippocampus (28). Although very effective, the use of ECT is partly restricted due to its cognitive side effects. Significant changes in cognitive functions related to treatment with ECT include impairment in episodic memory and executive functions (29). The hippocampus is known to be a key regulator in the consolidation of information from short-term to long-term memory (30). We recently presented data suggesting an immediate significant increase in hippocampal volume after treatment with ECT in depressed subjects (23). However, to the best of our knowledge, no systematic longitudinal studies have previously been carried out on the possible relation between changes in hippocampal volume and clinical and cognitive outcome in patients with depression treated with ECT.

Aims of the study

The aims were to study the longitudinal course of hippocampal volume over the course of a year after electroconvulsive therapy (ECT), and to determine whether changes in hippocampal volume were related to clinical and cognitive outcome.

We hypothesized that the increase in hippocampal volume seen after a course of ECT would be sustained after 6 and 12 months. We also hypothesized that the increase in volume would be positively related to the antidepressive effect and that it would be negatively correlated to performance in cognitive tests, with the emphasis on the episodic memory.

Material and methods

Psychiatric ratings, neuropsychological assessments and magnetic resonance imaging (MRI) were performed within the week before ECT (referred to as assessment point 1, A1), within the week after ECT (referred to as assessment point 2, A2), a minimum of 6 months after baseline (referred to as assessment point 3, A3) and a minimum of 12 months after baseline (referred to as assessment point 4, A4). The average time interval between A1 and A2 was 28 days (range, 16–37 days), between A1 and A3 was 7 months (range, 6–9 months) and between A1 and A4 was 13.5 months (range, 12–16 months).

Subjects

The subjects were consecutively recruited from in-patients referred for ECT by their psychiatrist at Lund University Hospital Psychiatry Clinic, Sweden. All patients had been clinically investigated including normal physical examination and routine blood sampling.

The participants were clinically examined by one of the authors (PN) before inclusion in the study.
Inclusion criteria were that they had to satisfy the diagnosis of a depressive episode (unipolar or bipolar) according to the Diagnostic and Statistical manual of Mental Disorder, fourth edition (DSM IV) (31) and the Mini International Structured Interview (MINI) (32). Exclusion criteria were ECT during the past 12 months, substance abuse, involuntary care, pregnancy, life-threatening somatic disease, inability to give informed consent or contraindication to MRI.

Twenty patients were recruited to the study at A1. Twelve completed the study to A2, 10 to A3 and 7 to A4. Reasons for dropping out of the study before A2 were as follows: three patients refused further MRI, three patients could not be assessed within 1 week of treatment, one patient was found to have a cardiac disease during the first ECT treatment and one only underwent three ECT treatments, then went into a manic state and did not accept further treatment. One patient was deceased before A3, and another one chose to discontinue the study. Two of the patients relapsed before A4 and received repeated treatment with ECT, while one refused the final MRI examination.

Demographic data concerning the subjects are given in Table 1. All patients showed normal MRI scans on all four occasions.

Patients continued to take their medication during ECT, which consisted of different antidepressants with add-on therapy; serotonin–norepinephrine reuptake inhibitors (9/12), selective serotonin reuptake inhibitors (7/12) and tricyclic antidepressants (1/12). Six patients were being treated with mood stabilizers (five with lamotrigine, carbamazepine or valproate, and one with lithium) and two with antipsychotics (haloperidol or flupenthixol). Ten of the subjects had used antidepressant medication for more than 6 months prior to inclusion and two <6 months. During the 12-month follow-up, all patients except one (who was taking no medication at all at A4) were taking antidepressant medication continuously. The medication being taken at A3 and A4 was the same as that at inclusion, apart from small individual adjustments in dosage.

The study was approved by the Regional Ethical Review Board at Lund University, and all participants provided written informed consent.

ECT procedure

Electroconvulsive therapy (SpECTrum 5000Q; MECTA Corp., Lake Oswego, OR, USA) was administered on 3 days a week at the Lund University Hospital ECT unit. Right unilateral, brief-pulse stimulation was applied to all patients except two, who also underwent bitemporal treatment (three right unilateral + 12 bitemporal in one patient and 11 unilateral + one bitemporal in the other). Thiopental was used to induce anaesthesia (4–6 mg/kg body weight, injected intravenously), and succinylcholine was used to ensure muscle relaxation (0.3–0.8 mg/kg body weight). The initial stimulus dose was set according to age and gender and then adjusted during the treatment period depending on seizure (monitored both with regard to the cerebral epileptic activity recorded by the encephalogram and the motoric seizure), treatment efficacy and side effects. The psychiatrist in charge made the decision regarding the total number of ECT treatments based on experienced clinical judgement; the study protocol did not interfere with that decision.

| Variable | A1 (n = 12) | A2 (n = 12) | A3 (n = 10/12) | A4 (n = 7/12) |
|----------|-------------|-------------|----------------|-------------|
| Female: Male | 10 : 2 | 8 : 2 | 6 : 1 | |
| Age at inclusion (years) | 40.3 (19–67) | 38.1 (19–67) | 40.7 (19–67) | |
| Age at first episode (years) | 25.9 (13–62) | 26.3 (13–62) | 28.1 (13–62) | |
| Episode duration (months) | 6.2 (1–15) | 5.6 (1–11) | 5.3 (1–11) | |
| Number of ECT | 10.2 (6–15) | 9.4 (6–13) | 8.3 (6–12) | |
| Hippocampal volume | | | | |
| Right | 3109 (431) | 3247 (463) | 3072 (423) | 3006 (550) |
| Left | 2905 (392) | 3054 (421) | 2939 (414) | 2835 (412) |
| Total | 6014 (801) | 6296 (875) | 6010 (830) | 5841 (957) |
| MADRS 0–60 | 38 (6) | 13 (10) | 13 (10) | 9 (7) |
| MADRS-S (8–54) | 34 (6) | 18 (13) | 19 (12) | 11 (8) |
| Executive functioning | | | | |
| TMT-B | 83.8 (57.8) | 84.9 (43.6) | 69.0 (36.9) | 65.1 (29.3) |
| Stroop test | 124.0 (32.5) | 119.3 (33.5) | 109.8 (24.7) | 110.1 (30.1) |
| Verbal fluency | 46.9 (16.0) | 38.1 (16.1) | 49.2 (13.1) | 52.3 (12.1) |
| Processing speed | | | | |
| Digit symbol | 53.0 (15.9) | 54.8 (16.9) | 67.7 (16.7) | 66.1 (19.7) |
| Digit span | 14.5 (3.7) | 15.2 (4.7) | 16.5 (4.0) | 14.6 (4.2) |
| TMT-A | 39.8 (30.5) | 34.1 (18.5) | 25.7 (8.8) | 27.1 (4.5) |
| Spatial problem-solving | | | | |
| RCT copying | 33.1 (2.6) | 33.8 (2.6) | | |
| Block design | 38.9 (10.7) | 42.3 (12.8) | | |

ECT, electroconvulsive therapy; MADRS, Montgomery–Asberg Depression Rating Scale; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; TMT, Trail Making Test.
Psychiatric rating and neuropsychological assessment

The severity of depression was rated using the Montgomery–Asberg Rating Scale (MADRS) for clinical rating (33) and self-rating (MADRS-S) (34). Remission was defined as a score of <10 points after treatment (35), response as a reduction in score of 50% or more, and partial response as a reduction of 25–49%. At A2, five of the 12 patients met the criteria for remission, three were responding, three were considered to be partial responders and one did not respond to the treatment. In 10 of the subjects, MADRS and MADRS-S ratings agreed completely regarding the criteria for response. Two patients rated themselves as partial responders, whereas the clinical rating was a responder.

The Rey Auditory Verbal Learning Test (RAVLT) was used to evaluate the different aspects of verbal episodic memory (30). RAVLT Immediate assesses the encoding of new verbal information, RAVLT Retention the total amount of learning, RAVLT Delayed assesses the long-term recall memory and, finally, we also assessed RAVLT Recognition. These tests are especially sensitive to hippocampal functioning, and it has been suggested that the left hippocampus is more involved than the right. Visual episodic memory was assessed by the Rey Complex Figure Test (RCFT) (30), in which the right hippocampus is believed to be more involved. The Trail Making Test B (TMT-B), the Stroop Test (also called the Colour Word Test) and Verbal Fluency (30) were used to assess executive functions. Digit Symbol, Digit Span (36) and Trail Making Test A (TMT-A) (30) were used to evaluate processing speed and attention/working memory. Spatial problem solving was performed with the Block Design Test (36) and RCFT copying. The tests were administered by a neuropsychologist on all four occasions, except for the Block Design Test and RCFT (according to the recommendations in the test manual).

MRI acquisition and postprocessing

All MRI examinations were performed with a 3T MRI scanner (Magnetom Allegra; Siemens AG, Erlangen, Germany). An axial T2-weighted fluid attenuation inversion recovery (FLAIR) sequence was obtained (repetition time TR/echo time TE = 10000 ms/101 ms, inversion time TI = 2500 ms, slice thickness 5 mm, field of view 230 mm, image matrix 320 × 256) to rule out pathological changes in the brain. A coronal 3D magnetization prepared rapid gradient echo (MPRAGE) sequence covering the entire brain was obtained for hippocampal volume measurements, using the following parameters: flip angle 8°, TR/TE = 2500 ms/4.38 ms, TI = 1100 ms, slice thickness 1 mm, field of view 256 mm, image matrix 256 × 256. The MPRAGE sequence was obtained perpendicular to the hippocampus. Sagittal 1 mm slices were reconstructed from this sequence through the whole brain after scanning. The maximal permitted angle discrepancy between the two coronal MPRAGE sequences from the same patient was 5°, as measured by the line between anterior and posterior commissure. If this value was exceeded, new oblique coronal 1-mm slices were reconstructed from the original coronal 3D volume.

Measurements of hippocampal volume

The hippocampus was manually delineated on the coronal slices using a graphics tablet (Wacom Co. Ltd. Kita Saitama-Gun, Saitama, Japan) together with a picture archiving and communication system (PACS) workstation. The area of each outlined region was calculated automatically. Standard atlases were used for anatomical guidelines (37, 38), together with the established criteria of Watson (39). The sagittal slices reconstructed from the coronal 3D volume were visualized simultaneously to improve the accuracy, especially with regard to delineation with the amygdala. Two raters, trained by experienced senior neuroradiologists, outlined both hippocampi before and after ECT. Reliability (kappa > 0.9) was established by repeated measurements on multiple MRI scans of subjects not included in the study. The raters were blinded to the clinical outcome, but the date of scanning was visible on the scans. The raters did not assess the scans in consecutive order according to subject or date of scanning. In the two assessments in the follow-up period the hippocampi were outlined by one of the two raters.

Statistical analysis

The small number of participants may be problematic in the statistical analysis. Parametric tests were used in all analyses (Pearson, dependent sample t-test). However, to check whether the low number of participants affected the results, all statistical analyses were also performed using nonparametric tests (Wilcoxon, Spearman). Comparison between the results of the parametric and nonparametric tests revealed no differences in significance/non-significance, and thus the use of parametric tests was deemed adequate in this study. Parametric
tests have the advantage that mean values can be used in the descriptive statistics.

**Results**

**Assessment of hippocampal volume 6 and 12 months after ECT**

Descriptive statistics are given in Table 1. As can be seen in Fig. 1, there was a significant increase in the volume of the hippocampus immediately after ECT (at A2) \( t(11) = 3.74, \ P < 0.01 \); \( t(11) = 6.58, \ P < 0.001 \) (23), which returned to baseline levels after 6 months; \( t(9) = -2.65, \ P < 0.05 \); left \( t(9) = -3.38, \ P < 0.01 \). There were no further significant changes after 1 year \( (A3 vs. A4) \), and no significant differences between A1 and A3 or between A1 and A4.

We therefore found no support for our hypothesis that the volume increase seen immediately after ECT was sustained after 6 or 12 months.

**Clinical outcome and hippocampal volume**

There was a significant reduction in both the clinical MADRS score \((A1 vs. A2, mean reduction: 24.8, SD 11.4, confidence interval 17.6–32.1, P < 0.001)\) and the self-rated MADRS-S score \((A1 vs. A2, mean reduction: 16.7, SD 9.0, confidence interval 10.9–22.4, P < 0.001)\) after ECT. No other significant changes were seen in the subjects participating during the follow-up (Table 1, Fig. 2). The reduction in the MADRS score between A1 and A2 was negatively correlated to the increase in volume of the right hippocampus \( (r = -0.58, P < 0.05) \). When adjustments were made for the number of ECT treatments and age, this correlation disappeared. No correlation was found between the MADRS score and the increase in volume of the left hippocampus. The increase in volume of the left hippocampus \((A1 vs. A2)\) was positively correlated to the number of ECT treatments \( (r = 0.67, P < 0.05) \), but no such correlation was found for the right hippocampus. Neither age nor gender showed any significant correlation with the increase in volume \((A1 vs. A2)\). No correlation was found between any changes in the MADRS score and the return to baseline levels of volume of the hippocampus at A3 and A4.

We therefore found no support for our hypothesis that the increase in hippocampal volume seen after a course of ECT is related to the antidepressive effect of the treatment.

**Cognitive outcome and hippocampal volume**

Results in stanine/scale points (relating to the normal distribution of performance) regarding episodic memory, executive functions and processing speed are illustrated in Figs 3–5. A decrease was found in RAVLT Immediate \([t(11) = -1.90, n.s.], RAVLT Retention \([t(11) = -2.82, P < 0.05], RAVLT Delayed \([t(11) = -3.22, P < 0.01] \) and RAVLT Recognition \([t(11) = -2.39, P < 0.05] \) immediately after ECT (i.e. between A1 and A2). This reduction was reversed at A3 (i.e. between A2 and A3): RAVLT Immediate \([t(9) = 1.81, n.s.], RAVLT Retention \([t(9) = 2.94, P < 0.05], and RAVLT Recognition \([t(9) = 2.33, P < 0.05] \), showing non-significant differences compared with baseline levels (i.e. between A1 and A3). According to RAVLT Delayed, a return to baseline levels close to significance was seen at A3 \([t(9) = 2.21, P = 0.054] \), but a true significant reversion of the
decrease at A2 lasted until A4 \( t(6) = 3.04, P < 0.05 \). Two of the tests related to executive functions (TMT-B and Verbal Fluency) also showed a transient decrease at A2, reaching significance in Verbal Fluency, \( t(11) = -2.81, P < 0.05 \). At the follow-up assessments, there was a significant improvement in executive functions at A3 compared with baseline according to the Stroop test \( t(9) = 3.35, P < 0.01 \), and at A4 according to TMT-B \( t(6) = 3.82, P < 0.01 \). No differences were found in Verbal Fluency between the follow-up assessments and the baseline levels. Performance in tests related to processing speed and attention/working memory, on the other hand, showed a trend towards improvement at A2 (Table 1, Fig. 5). Furthermore, the results of the Digit Symbol Test were significantly improved at A3 compared with baseline \( t(9) = 3.59, P < 0.01 \), as was TMT-A \( t(9) = 2.83, P < 0.05 \).

No significant long-term effects were observed in the RCFT or Block Design Test.

The increase in left hippocampal volume immediately after ECT (A1 vs. A2) was significantly correlated to an improvement in the TMT-A score \( r = 0.64, P < 0.05 \), but after adjusting for the number of ECT treatments, this correlation disappeared. No other cognitive tests were associated with changes in hippocampal volumes, or the number of ECT treatments.

We therefore found no support for our hypothesis that performance in cognitive tests could be related to changes in hippocampal volume.

**Discussion**

The main finding of this study was that the significant increase in the volume of the hippocampus in
patients with depression treated with ECT returns to baseline levels after 6 months and that no further changes are seen after 12 months.

The transient volume changes found in the present study could possibly be explained by a transient oedema. However, oedema is often visible on MRI, and we found no evidence of oedema in the hippocampus on T2-weighted FLAIR images. Kunigiri et al. (40), detected no increase in T2 relaxation time (corresponding to water content) in the hippocampus after ECT, suggesting that hippocampal oedema does not result from ECT.

There is a great deal of evidence from preclinical studies that cell proliferation occurs in the hippocampus as a result of many different methods of antidepressive treatment, including electroconvulsive stimulation (ECS) (14). Neurogenesis is not the only effect. Increases in neuropil, glial cell activation and angiogenesis have also been reported (17, 19, 41), which could produce a volume increase visible with MRI. In a recent animal study, Kaee et al. (41) showed that ECS induced a detectable increase in hippocampal volume, accompanied by a corresponding increase in the number of neurons and glial cells, indicating that the volume increase seen immediately after ECT in humans may be due to morphological changes and not oedema.

If the volumetric increase seen in this study is caused by cell proliferation, the return to the pretreatment volume must be explained by a contrary mechanism. The initial treatment-induced burst of proliferation may decrease via normal pruning and migration mechanisms. But recent findings indicate that constitutional dysfunction in critical mediators of neuroprotective and synaptic plasticity processes, especially the Brain Derived Neurotrophic Factor, might contribute to the development of depression (42). The volume decrease may thereby represent a trait-dependent vulnerability of the patients to depression, taking place before recurrence of the disease. Clinical studies have also shown that a family history of depression and early-life stress without any depressive episodes are associated with lower hippocampal volume (43, 44). Another, or simultaneous, mechanism of the volume decrease maybe the well-known link between hypercortisolaemia in stress and depression (2), causing structural changes in the hippocampus (45) and in gross structures in the brain (46). This stress-induced alteration may represent a state-dependent factor which is reversible.

At clinical level, our findings highlight the question of whether hippocampal volume is of importance for the antidepressive efficacy of the treatment. We found a significant improvement in the MADRS score in this study, but no significant correlation was found between this improvement and the individual increase in hippocampal volume. Before adjusting for the number of ECT treatments, the correlation even seemed to be negative in the right hippocampus. This was unexpected and is not easily explained. One explanation could be that a subject not responding to ECT will undergo more treatments than a subject who responds, before the decision is made to stop the treatment. If the treatment itself, that is the numbers of ECT, causes the volume increase, without any relation to the antidepressive effect, individuals who respond less should show a greater increase in hippocampal volume. However, we only found a correlation between the number of ECT treatments and the increase in volume of the left hippocampus. Our results support the findings of Frodl et al. (20) and Schermule et al. (21), who found that an increase in hippocampal volume was associated only with treatment with pharmacological antidepressants and that there was no significant correlation to response rate.

The question of whether ECT could cause permanent morphological changes in the brain has been an important one in the field of psychiatric research. In the present study, the detectable change in the size of hippocampus immediately after ECT was transient, which is in line with previous studies in which ECT caused no permanent structural changes in the brain (47, 48).

The present findings also confirm the well-documented outcome of ECT as a significant, effective form of treatment for depression (27), albeit causing significant acute impairment of the verbal episodic memory (29). In the present study, cognitive functions related to attention and processing speed tended to improve immediately after ECT, in contrast to mental flexibility and verbal fluency, which tended to decrease. This could be of importance when addressing the question of differences in subjective and objective memory in ECT research (49). A correlation between the score in episodic memory tests and changes in hippocampal volume is theoretically plausible, due to the importance of the hippocampus in episodic memory. We found an overall significant decrease in verbal episodic memory scores up to a week after ECT, together with an increase in hippocampal volume, but the two were not significantly correlated. Neither was the reversal of this impairment 6 and 12 months later correlated to the return of hippocampal volume to the baseline level. In another study, Vythilingam et al. (24) found that patients successfully
treated with antidepressants showed significant improvement in tests of verbal episodic memory without any significant changes in hippocampal volume; the time between assessments in their study was 7 months.

The usefulness of ECT is claimed to be restricted due to its cognitive side effects and the question of whether they are fully reversible or not (50). In the present study, none of the cognitive domains showed persistent impairment at the end of the follow-up period, 12 months later. Indeed, we found the cognitive side effects to be reversed after 6 months. A recent meta-analytic review revealed that no significant cognitive side effects related to ECT were found after 15 days (29). It is, therefore, possible that the recovery of cognitive functions occurs earlier than 6 months.

To the best of our knowledge, this is the first longitudinal study over a 1-year period of the relation between changes in hippocampal volume and clinical and cognitive outcome in patients with depression treated with ECT. The results suggest a transient treatment-induced increase in hippocampal volume, with no state-dependent relation with treatment efficacy or cognitive side effects. However, these findings should be treated with caution as they are based on a small sample. In addition, an observational study always includes a high risk of random bias. The sample included patients with a wide range of ages and patients with both unipolar and bipolar depression. Also, it is not possible to characterize the different internal components constituting the hippocampal volume using volumetric measurements based on MRI. Despite these limitations, we believe we have made advances in translating core concept findings from animal studies to humans with depression, which are valuable in elucidating the biological model of conceptualizing depression.

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Declarations of interest

None.

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