Brain Stimulation 14 (2021) 1330–1339

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Short and long-term effects of single and multiple sessions of electroconvulsive therapy on brain gray matter volumes

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ARTICLE INFO

Article history:
Received 24 March 2021
Received in revised form
16 August 2021
Accepted 19 August 2021
Available online 28 August 2021

ABSTRACT

Background: Electroconvulsive therapy (ECT) has been shown to induce broadly distributed cortical and subcortical volume increases, more prominently in the amygdala and the hippocampus. Structural changes after one ECT session and in the long-term have been understudied.
Objective: The aim of this study was to describe short-term and long-term volume changes induced in cortical and subcortical regions by ECT.
Methods: Structural brain data were acquired from depressed patients before and 2 h after their first ECT session, 7–14 days after the end of the ECT series and at 6 months follow up (N = 34). Healthy, age and gender matched volunteers were scanned according to the same schedule (N = 18) and patients affected by atrial fibrillation were scanned 1–2 h before and after undergoing electrical cardioversion (N = 16). Images were parcelled using FreeSurfer and estimates of cortical gray matter volume and subcortical volume changes were obtained using Quarc.
Results: Volume increase was observable in most of gray matter regions after 2 h from the first ECT session, with significant results in brain stem, bilateral hippocampi, right putamen and left thalamus, temporal and occipital regions in the right hemisphere. At the end of treatment series, widespread significant volume changes were observed. After six months, the right amygdala volume was still significantly increased. No significant changes were observed in the comparison groups.
Conclusions: Volume increases in gray matter areas can be detected 2 h after a single ECT session. Further studies are warranted to explore the underlying molecular mechanisms.

1. Introduction

The efficacy of electroconvulsive therapy (ECT) in the treatment of severe mood disorders has been repeatedly confirmed and has been widely recognized in international guidelines. However, it is still not clear which mechanisms underlie response to ECT. Generalized and repeated seizures, likely affecting centrencephalic and prefrontal regions, may represent a necessary, yet not sufficient condition for ECT efficacy, as early suggested by the efficacy of chemically induced generalized seizures and the positive associations between ictal EEG indices and therapeutic outcomes [1,2]. While both bitemporal and high-dose right unilateral ECT have showed the same efficacy, low- and moderate-dose unilateral stimulation, which also produce generalized seizures, are less effective [3,4]. More recently, current paths and density have gained more attention and the recruitment of a sufficiently large

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https://doi.org/10.1016/j.brs.2021.08.018

neuronal population in prefrontal cortex in seizure initiation has been hypothesized to underlie ECT antidepressant efficacy [5,6].

Several biological models have been proposed to explain the clinical effects of ECT. The main current theories of the mechanism of ECT could be subsumed into at least three different, although partially overlapping, classes, based on the relevance which is respectively given to: 1) changes in neurotransmission and endocrine signals induced by diencephalic stimulation [1,7,8]; 2) changes in inflammation cascade in the CNS via immune system modulation [9–11]; 3) induced neurotrophic effects, including neurogenesis, synaptogenesis, angiogenesis, glial cell proliferation [1,11,12].

Studies mainly conducted in animal models of electroconvulsive stimulation (ECS) demonstrated that electrically induced seizures can increase hippocampal neurogenesis and synaptogenesis, induce vascular growth and glial cell proliferation, and modulate BDNF expression [11–15]. Human studies, although underpowered and heterogenous, consistently showed higher amygdala and hippocampus volumes after a series of ECT treatments [16], and occasionally volume increases in the anterior cingulate gyrus, insula and temporal cortex were shown [17]. More recently, cortical and subcortical volume increases after an ECT course were found to be broadly distributed across the brain in a mega-analysis of 328 depressed patients through the Global ECT-MRI Research Collaboration (GEMRIC) [18]. Interestingly, changes were maximal in the amygdala and the hippocampus and were prominent in regions closest to the temporal electrodes. Further, they were positively associated with the number of ECT treatments and were greater in subcortical regions in patients receiving bilateral stimulation, but no association was found with clinical outcome [18]. As the author suggested, “despite co-occurring neuroplastic and molecular effects, only the molecular effects may be a key mechanism underlying the therapeutic success of ECT”, with volume increases possibly representing an epiphenomenon [18] and largely explained by the magnitude of the electrical field [19].

On the other hand, volume changes induced immediately after one ECT session have been understudied. Previous studies found significantly increased hippocampus and amygdala volumes bilaterally after the second ECT session, with further increases in volumes after the end of ECT treatment [20], while no significant changes in cortical thickness or subcortical volumes were found nor after the first [21] or the second ECT session [22,23]. In order to evaluate whether widespread volume increases were present immediately after a single ECT session and whether they persisted in the long-term after a series of treatments, depressed patients receiving ECT were recruited and scanned before (N = 34) and after (N = 33) their first session, 7–14 days after the end of series (N = 29) and at 6 months follow up (N = 22).

2. Materials and methods

2.1. Participants, ECT procedure and assessments

The study protocol has been detailed elsewhere [24], a brief summary is given here. Patients were recruited among individuals accepted for ECT at Haukeland University Hospital, Bergen, Norway. Eligibility required patients to be adults (age >18 years), referred to the ECT-unit and accepted for treatment because of moderate or severe depressive episode with a score ≥25 on the Montgomery and Åsberg Depression Rating Scale (MADRS), both unipolar and bipolar depressive disorder. ECT treatment within the last 12 months, pregnancy, inability to give written informed consent (according to the responsible clinician or ECT responsible) and contraindications to MRI were considered as exclusion criteria. During the study period, 352 ECT series were performed at our treatment unit. All patients were screened for participation in the study. The main reasons for non-inclusion were technical (MRI not available) or meeting one of the exclusion criteria. Of patients who were eligible and asked for inclusion, 27 did not want to participate in the study. Out of 34 included patients who completed the baseline MRI 22 also completed the MRI at the 6 months follow up time point.

ECT was administered with a Thymatron System IV (Somatics LLC, Venice, FL, USA) providing brief-pulse (0.5 ms), square wave, constant current. All patients received treatment with right unilateral electrode positioning (RUL). However, one patient was transitioned to bitemporal ECT after 14 treatments because initial RUL sessions were not effective. Anesthesia was obtained with the short acting anesthetic thiopental and succinylcholine was used for muscular blockade. The initial stimulus energy was determined based on age and gender. The initial charge was determined by an age-based method with patient's age in years x 5 ≅ stimulus charge expressed in millicoulombs (mC). In order to consider gender specific differences in seizure threshold, the % Energy was adapted as following: For male patients: % Energy +5–10%. For female patients: % Energy −5 to 10%. Usually, three sessions per week were given until clinical remission.

Healthy, age and gender matched volunteers were recruited for repeated magnetic resonance imaging (MRI) to account for repeated measurements/time effects on imaging parameters. To control for the potential effect of anesthesia on MRI, patients receiving propofol for electrical cardioversion (ECV) for atrial fibrillation were recruited.

Depressed patients received MRI scanning at four separate time points: 1–2 h before (median = 8:00 a.m., T1, N = 34) and 1–2 h after the first ECT session (median = 12:00 p.m., T2, N = 33), 7–14 days after the end of the ECT series (T3, N = 29) and at follow-up 6 months after (T4, N = 22). Data from T1 and T3 scans of ECT patients were previously included in GEMRIC mega-analysis [18]. Healthy controls (HC) were scanned four times at intervals similar to the patients (N = 18 at T1-T2, N = 16 at T3-T4). Patients receiving ECV (N = 16) were scanned twice: before (median = 8:50 a.m.) and after ECV (median = 3:15 p.m.).

Clinical evaluations for patients receiving ECT were performed at baseline, T3 and T4. Depression severity was estimated using MADRS. Cognitive side effects were assessed using the Everyday Memory Questionnaire (EMQ), a self-reported inventory of subjective memory complaints, and consistency scores based on the Autobiographical Memory Interview-Short Form (AMI-SF), as previously detailed [25].

All participants provided written informed consent and the study were approved by the Regional Committee for Medical and Health Research Ethics, REC South East, Norway (2013/1032).

2.2. Image acquisition and processing

Structural data were acquired on a 3 T Discovery MR750 system with 32-channel head coil. The protocol included a T1-weighted fast spoiled gradient echo, FSPGR (TE/TR = 2.9/6.7 ms; TI = 600 ms, flip angel = 8°; FOV = 25.6 cm; voxel size = 1.0 × 1.0 × 1.0 mm^3, acquisition time = 10:32 min). Seven ECT patients and one HC were scanned on a 3 T GE Signa HDxt equipped with an 8-channel head coil. The protocol included a T1-weighted inversion recovery spoiled gradient echo sequence, IR SPGR (TE/TR = 2.8/6.5 ms; TI = 450 ms; flip angle = 8°; FOV 256 mm; voxel size = 1.0 × 1.0 × 1.0 mm^3). Images were corrected

for distortions caused by gradient non-linearity [26] and then processed using automated FreeSurfer preprocessing steps (version 5.3; surfer.nmr.mgh.harvard.edu/), which includes segmentation of subcortical white matter, deep gray matter structures and automated parcellation of the cerebral cortex [27–30]. Unbiased, within-subject assessment of longitudinal changes of regional brain volumes was performed using Quarc [31–33]. The image processing pipeline corrects for scanner-specific distortions [26] and maximizes power for longitudinal change estimation while avoiding bias [33–35]. Estimates of relative volume change (%) between T1 and T2, T3 and T4, were respectively obtained for each region of interest (ROI) for each subject.

2.3. Statistical analysis

Differences between depressed patients and HC in age and gender were first checked, respectively using two samples t-test, after normality check using Shapiro-Wilk, and chi-squared test. Single sample t-tests were conducted to determine if volume change estimates at T2, T3 and T4 were statistically significantly different from 0 in each of the groups for each of the ROIs. Since single sample t-tests were performed on intra-individual volume change estimates, no between-subject nuisance variable was considered. False discovery rate (FDR) correction for multiple comparisons was applied.

Significant changes were then compared among the groups using analysis of variance (ANOVA) with Tukey's honest significance test for post-hoc analysis at T2 and two-sample t-tests at T3 and T4.

In addition, we tested whether volume changes observed in ECT patients at T3 could be predicted by changes at T2 using three different linear models for each region with the following variables included as predictors: i) volume changes at T2 (unadjusted model); ii) volume changes at T2, number of ECT sessions (adjusted model); iii) volume changes at T2, number of ECT sessions and the interaction between these predictors (interaction model). A linear model was also used to test whether volume changes in ECT patients at T4 were predicted by changes at T3, without controlling for other variables. False discovery rate (FDR) correction for multiple comparisons was again applied to linear models.

Cross-sectional comparisons between depressed patients and HC ROIs' volumes were performed at each time point using a linear model of ROI volume with group, age, gender, total intracranial volume and scanner as predictors, applying false discovery rate (FDR) correction.

Finally, for the ROIs with significant longitudinal volume changes, we performed post-hoc exploratory correlation analyses between i) volume change and change in depression severity ($MADRS_{T3-T1}$, $MADRS_{T4-T1}$), ii) volume change and changes in subjective memory complaints (EMQ_{T3-T1}, EMQ_{T4-T1}) and iii) volume change and autobiographical memory (AMI-SF $consistency_{T3}$, AMI-SF $consistency_{T4}$) by using linear regression models both with and without the total number of ECT sessions as a predictor. Specifically, volume changes were correlated with MADRS change, EMQ change and AMI-SF consistency at T3 for ROIs with significant volume change between T1 and T2 or T3, and at T4 for ROIs with significant changes between T1 and T4.

Since MRI data from four patients and one HC were acquired with different devices at T1 and T4, those subjects were excluded from all the analyses on volume change estimates at T4. Results associated with $p < 0.05$ were considered significant. All statistical analyses were performed using R Statistical Software, version 3.6.0 (Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Samples characteristics

Depressed patients and HC did not differ significantly in age (46.42 ± 15.18 vs. 42.83 ± 15.88, $t = 0.79$, $p = 0.44$) and in gender (females 18/34, 53%, vs. 11/18, 61%, $\chi^2 = 0.07$, $p = 0.79$). ECV controls were more frequently males (females 1/16, 6.3%, $\chi^2 = 8.18$, $p = 0.004$) and older aged (mean ± SD = 66.50 ± 6.3, $t = 6.22$, $p < 0.001$) in comparison with depressed patients included in the study (Table 1).

3.2. Longitudinal effects

Depressed patients treated with ECT showed significant volumetric increases in several cortical and subcortical regions at T2, T3 and T4 ($p_{FDR} < 0.05$) (Fig. 1A, Table 2). After the first ECT session (T2), the brain stem, the bilateral hippocampi, left thalamus proper, right putamen, right inferior lateral ventricle, right banks of the superior temporal sulcus, right lateral occipital cortex, right lingual gyrus and right middle temporal gyrus showed significant volume increases as compared with baseline volumes.

After the end of the treatment series (T3), significant changes were broadly distributed both in cortical and subcortical regions ($p_{FDR} < 0.05$). In the cortex, all regions showed significant increases, except for bilateral frontal poles, left medial and lateral orbitofrontal cortex, left pars orbitalis of the inferior frontal gyrus, right isthmus cingulate and pericalcarine cortex. Among subcortical regions, thalamus, caudate, putamen, pallidum, hippocampus, amygdala and nucleus accumbens volumes were bilaterally increased, while ventral diencephalon volume increase was significant only on the right side. No significant changes were demonstrated for cerebral white matter, cerebellum white matter and cortex and brain stem volumes at T3. All the ventricles, except the fourth, showed significant volume decreases. After six months from the end of the treatment (T4), the right amygdala volume increase was still significant after FDR correction, while left amygdala, entorhinal cortex bilaterally, right temporal pole and right lateral ventricle showed significant increases at the uncorrected level (see Table 2).

HC did not show significant volume changes after FDR correction at any time point (Fig. 1B, Supplementary Table 1). Similarly, patients treated with ECV did not show significant volume changes after correction for multiple comparisons (Supplementary Table 2).

3.3. Longitudinal comparisons

Among significant volumetric increases observed in depressed patients after the first ECT session (T2), changes in the brain stem, in right inferior lateral ventricle and in the right banks of the superior temporal sulcus were significantly greater than in HC and ECV controls. In addition, changes in left thalamus proper, right lateral occipital cortex and right middle temporal gyrus were significantly greater than in HC, while changes in left hippocampus and right putamen were significantly greater than in ECV controls. Right hippocampus and right lingual gyrus and changes were not significantly different among groups (Table 3). No significant changes between HC and ECV controls were observed.

Table 1
Characteristics of the samples.

		ECT patients	*n*	HC	*n*	ECV patients	*n*
Age	*Mean (SD)*	46.42 (15.18)	34	42.83 (15.88)	18	65.50 (6.48)	16
Sex	*Females (%)*	18 (52.9)	34	11 (61.1%)	18	1 (6.3%)	16
T1 (time of day, hours)	*Median (IQR)*	8.00 (0.17)	34	8.00 (0.00)	18	8.83 (0.42)	16
T2 (time of day, hours)	*Median (IQR)*	12.00 (0.00)	33	12.00 (0.00)	18	15.15 (0.25)	16
T3 (time of day, hours)	*Median (IQR)*	9.25 (2.00)	29	8.00 (1.63)	16	–	
T4 (time of day, hours)	*Median (IQR)*	9.00 (1.69)	22	8.08 (1.75)	16	–	
T2-T1 (hours)	*Median (IQR)*	4.00 (0.17)	33	4.00 (0.00)	18	6.48 (0.36)	16
T3-T1 (days)	*Mean (SD)*	39.93 (15.26)	29	46.88 (14.15)	16	–	
T4-T1 (days)	*Median (IQR)*	207 (37)	22	202.33 (20.10)	16	–	
Episode duration (months)	*Median (IQR)*	8.25 (14.65)	32	–		–	
ECT sessions (number)	*Mean (SD)*	10.97 (4.11)	32	–		–	
$MADRS_{T1}$	*Mean (SD)*	33.59 (4.94)	34	–		–	
$MADRS_{T3}$	*Mean (SD)*	15.40 (8.32)	33	–		–	
$MADRS_{T4}$	*Mean (SD)*	14.45 (12.09)	20	–		–	
Antidepressants	*Number using during ECT (%)*	23 (68)	34				
Antipsychotics	*Number using during ECT (%)*	23 (68)	34				
Antiepileptics	*Number using during ECT (%)*	3 (8.8)	34				
Lithium salts	*Number using during ECT (%)*	3 (8.8)	34				
Benzodiazepines	*Number using during ECT (%)*	1 (2.9)	34				
ECT charge at first treatment (mC)	*Mean (SD)*	228 (84)	34				
ECT charge at last treatment (mC)	*Mean (SD)*	253 (108)	34				
Response ($MADRS_{T3}$ change $\geq$ 50%)	*Number at T3 (%)*	20 (60.6)	33				
Remission ($MADRS_{T3}$ < 10)	*Number at T3 (%)*	11 (33.3)	33				
Psychotic depression	*Number at inclusion (%)*	3 (8.8)	34				
Bipolar depression	*Number at inclusion (%)*	7 (21)	34				

Many significant volumetric changes observed within two weeks after the end of the ECT series in depressed patients, were significantly different from those observed in HC at the same timepoint (T3). All the volumetric increases in subcortical regions were greater in ECT patients than in HC, except than for the left pallidum changes whose difference only approached statistical significance ($p = 0.078$). Similarly, all the volumetric decreases in the ventricles were significantly more pronounced in ECT patients than in HC. In the right hemisphere approximately two thirds of volume increases observed after ECT were significantly greater than in HC. Frontal and parietal gyri, the cuneus, precentral and supramarginal gyri made exceptions (Table 3). Conversely, statistically significant differences in left hemisphere were found only for caudal anterior and posterior cingulate cortex, cuneus, entorhinal

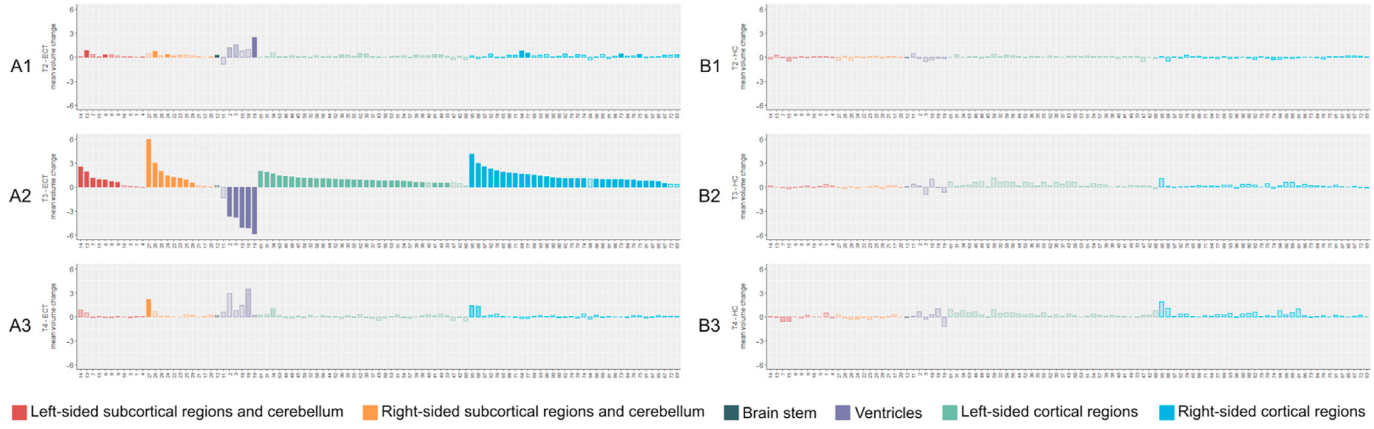

Fig. 1. Mean volume changes (%) from baseline approximately 2 h after the first ECT session (T2, 1), one week after the end of ECT course (T3, 2) and six months after (T4, 3) in ECT patients (A) and HC (B). Significant findings which survived FDR correction are highlighted in opaque colours, significant findings which did not survive FDR correction are shown with low transparency, not significant changes with high transparency. ***Abbreviations:*** *L = left; R = right; Lh = left cortical hemisphere; Rh = right cortical hemisphere.* ***Legend:*** *1 = L cerebral white matter; 2 = L lateral ventricle; 3 = L* inf *lat vent; 4 = L cerebellum white matter; 5 = L cerebellum cortex; 6 = L thalamus proper; 7 = L caudate; 8 = L putamen; 9 = L pallidum; 10 = third 3rd ventricle; 11 = forth* 4th *ventricle; 12 = brain stem; 13 = L hippocampus; 14 = L amygdala; 15 = L accumbens area; 16 = L ventraldc; 17 = R cerebral white matter; 18 = R lateral ventricle; 19 = R* inf *lat vent; 20 = R cerebellum white matter; 21 = R cerebellum cortex; 22 = R thalamus proper; 23 = R caudate; 24 = R putamen; 25 = R pallidum; 26 = R hippocampus; 27 = R amygdala; 28 = R accumbens area; 29 = R ventraldc; 30 = Lh bankssts; 31 = Lh caudalanteriorcingulate; 32 = Lh caudalmiddlefrontal; 33 = Lh cuneus; 34 = Lh entorhinal; 35 = Lh fusiform; 36 = Lh inferiorparietal; 37 = Lh inferiortemporal; 38 = Lh isthmuscingulate; 39 = Lh lateraloccipital; 40 = Lh lateralorbitofrontal; 41 = Lh lingual; 42 = Lh medialorbitofrontal; 43 = Lh middletemporal; 44 = Lh parahippocampal; 45 = Lh paracentral; 46 = Lh parsopercularis; 47 = Lh parsorbitalis; 48 = Lh parstriangularis; 49 = Lh pericalcarine; 50 = Lh postcentral; 51 = Lh posteriorcingulate; 52 = Lh precentral; 53 = Lh precuneus; 54 = Lh rostralanteriorcingulate; 55 = Lh rostralmiddlefrontal; 56 = Lh superiorfrontal; 57 = Lh superiorparietal; 58 = Lh superiortemporal; 59 = Lh supramarginal; 60 = Lh frontalpole; 61 = Lh temporalpole; 62 = Lh transversetemporal; 63 = Lh insula; 64 = Rh bankssts; 65 = Rh caudalanteriorcingulate; 66 = Rh caudalmiddlefrontal; 67 = Rh cuneus; 68 = Rh entorhinal; 69 = Rh fusiform; 70 = Rh inferiorparietal; 71 = Rh inferiortemporal; 72 = Rh isthmuscingulate; 73 = Rh lateraloccipital; 74 = Rh lateralorbitofrontal; 75 = Rh lingual; 76 = Rh medialorbitofrontal; 77 = Rh middletemporal; 78 = Rh parahippocampal; 79 = Rh paracentral; 80 = Rh parsopercularis; 81 = Rh parsorbitalis; 82 = Rh parstriangularis; 83 = Rh pericalcarine; 84 = Rh postcentral; 85 = Rh posteriorcingulate; 86 = Rh precentral; 87 = Rh precuneus; 88 = Rh rostralanteriorcingulate; 89 = Rh rostralmiddlefrontal; 90 = Rh superiorfrontal; 91 = Rh superiorparietal; 92 = Rh superiortemporal; 93 = Rh supramarginal; 94 = Rh frontalpole; 95 = Rh temporalpole; 96 = Rh transversetemporal; 97 = Rh insula. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)*

Table 2
Patients' volume changes from baseline approximately 2 h after the first ECT session (T2), one week after the end of ECT course (T3) and six months after (T4). Significant findings which survived FDR correction are highlighted in bold. Legend numbers from Fig. 1 are also reported (#). *Abbreviations: ROI = region of interest; SD = standard deviation; L = left; R = right; Lh = left cortical hemisphere; Rh = right cortical hemisphere.*

ROI		T2 (N = 33)				T3 (N = 29)				T4 (N = 18)			
		Volume change (%)		One-sample *t*-test		Volume change (%)		One-sample *t*-test		Volume change (%)		One-sample *t*-test	
	#	Mean	SD	t	p	Mean	SD	t	p	Mean	SD	t	p
L cerebral white matter	1	0.00	0.33	0.05	0.956	0.05	0.51	0.49	0.626	0.07	0.52	0.61	0.552
L cerebellum white matter	4	0.07	0.47	0.90	0.372	−0.05	0.51	−0.57	0.573	0.07	0.63	0.51	0.619
L cerebellum cortex	5	0.08	0.32	1.42	0.166	0.11	0.59	1.01	0.320	−0.10	0.85	−0.49	0.632
L thalamus proper	6	0.29	0.56	3.01	**0.005**	0.90	0.81	5.99	**0.000**	−0.10	0.61	−0.71	0.490
L caudate	7	0.39	0.91	2.49	0.018	1.14	1.30	4.73	**0.000**	−0.13	1.09	−0.49	0.633
L putamen	8	0.31	0.60	2.93	0.006	0.70	1.01	3.74	**0.001**	−0.12	0.88	−0.57	0.574
L pallidum	9	0.23	0.93	1.44	0.161	0.58	0.78	4.04	**0.000**	0.03	0.83	0.17	0.867
L hippocampus	13	0.86	1.36	3.65	**0.001**	1.95	1.97	5.33	**0.000**	0.48	1.41	1.44	0.169
L amygdala	14	0.09	1.90	0.26	0.793	2.53	2.48	5.49	**0.000**	0.86	1.36	2.68	0.016
L accumbens area	15	0.03	1.49	0.12	0.907	0.97	2.22	2.35	**0.026**	0.07	1.88	0.16	0.878
L ventraldc	16	0.10	0.80	0.70	0.488	0.23	0.76	1.65	0.109	0.01	0.78	0.05	0.958
R cerebral white matter	17	0.01	0.30	0.21	0.836	0.11	0.49	1.15	0.258	0.03	0.53	0.25	0.804
R cerebellum white matter	20	0.06	0.40	0.93	0.359	0.07	0.48	0.73	0.472	0.22	0.58	1.61	0.125
R cerebellum cortex	21	0.13	0.49	1.46	0.153	0.15	0.63	1.27	0.215	−0.01	1.04	−0.03	0.975
R thalamus proper	22	0.22	0.58	2.15	0.039	1.22	1.19	5.52	**0.000**	0.02	0.84	0.10	0.925
R caudate	23	0.26	0.59	2.52	0.017	1.12	1.22	4.91	**0.000**	−0.02	0.98	−0.09	0.930
R putamen	24	0.40	0.55	4.16	**0.000**	1.45	1.00	7.75	**0.000**	0.12	0.86	0.57	0.573
R pallidum	25	0.26	0.89	1.67	0.104	0.90	1.03	4.70	**0.000**	0.31	0.81	1.62	0.124
R hippocampus	26	0.73	1.20	3.51	**0.001**	2.99	1.88	8.54	**0.000**	0.65	1.43	1.93	0.070
R amygdala	27	0.43	1.45	1.69	0.101	6.04	3.35	9.70	**0.000**	2.18	1.56	5.94	**0.000**
R accumbens area	28	0.23	1.54	0.86	0.394	1.97	2.51	4.23	**0.000**	0.09	1.58	0.24	0.810
R ventraldc	29	0.22	0.64	1.96	0.059	0.53	0.91	3.15	**0.004**	0.21	0.82	1.09	0.293
brain stem	12	0.29	0.45	3.73	**0.001**	0.21	0.72	1.60	0.122	0.16	0.82	0.83	0.420
L lateral ventricle	2	1.17	3.10	2.17	0.037	−3.68	7.74	−2.56	**0.016**	2.95	6.25	2.01	0.061
L inf lat vent	3	1.56	4.38	2.05	0.048	−3.77	7.70	−2.64	**0.013**	0.79	5.64	0.60	0.558
R lateral ventricle	18	0.95	3.21	1.69	0.100	−5.10	7.47	−3.68	**0.001**	3.49	5.94	2.50	0.023
R inf lat vent	19	2.50	4.06	3.53	**0.001**	−5.91	12.39	−2.57	**0.016**	0.23	3.68	0.26	0.798
3rd ventricle	10	0.83	3.84	1.24	0.225	−5.06	7.57	−3.60	**0.001**	1.46	5.64	1.09	0.289
4th ventricle	11	−0.87	3.79	−1.32	0.196	−1.36	4.40	−1.66	0.108	0.61	3.09	0.84	0.412
Lh banks sts	30	0.45	0.92	2.80	0.009	0.88	1.23	3.86	**0.001**	−0.11	1.31	−0.36	0.723
Lh caudal anterior cingulate	31	0.11	1.23	0.52	0.603	1.87	1.26	7.97	**0.000**	0.32	1.15	1.17	0.256
Lh caudal middle frontal	32	−0.03	0.86	−0.23	0.816	1.13	1.68	3.61	**0.001**	0.23	1.61	0.60	0.559
Lh cuneus	33	0.17	0.6	1.60	0.119	0.53	0.75	3.82	**0.001**	0.17	0.74	0.96	0.350
Lh entorhinal	34	0.51	2.73	1.08	0.289	1.66	2.45	3.64	**0.001**	1.00	1.49	2.85	0.011
Lh fusiform	35	0.28	0.94	1.69	0.101	0.98	1.06	4.94	**0.000**	0.15	0.89	0.70	0.494
Lh inferior parietal	36	0.32	0.76	2.46	0.019	0.98	1.39	3.80	**0.001**	−0.25	1.56	−0.67	0.513
Lh inferior temporal	37	0.08	0.84	0.54	0.592	0.83	1.23	3.66	**0.001**	−0.22	1.23	−0.76	0.458
Lh isthmus cingulate	38	0.21	0.92	1.31	0.200	0.57	1.12	2.77	**0.010**	0.14	1.00	0.61	0.547
Lh lateral occipital	39	0.29	0.66	2.51	0.017	0.61	0.94	3.49	**0.002**	−0.01	0.99	−0.06	0.954
Lh lateral orbitofrontal	40	0.21	1.09	1.10	0.279	0.55	1.44	2.07	0.048	0.32	1.12	1.23	0.237
Lh lingual	41	0.38	0.76	2.85	0.008	0.55	0.67	4.38	**0.000**	0.14	0.82	0.70	0.491
Lh medial orbitofrontal	42	0.13	0.73	1.02	0.315	0.42	1.11	2.01	0.054	−0.03	0.85	−0.16	0.876
Lh middle temporal	43	0.03	1.07	0.16	0.870	0.81	1.59	2.77	**0.010**	−0.43	1.23	−1.47	0.161
Lh parahippocampal	44	0.15	0.97	0.87	0.392	1.09	1.43	4.12	**0.000**	0.04	0.85	0.19	0.854
Lh paracentral	45	0.08	0.83	0.52	0.605	1.19	1.22	5.26	**0.000**	0.10	1.31	0.34	0.742
Lh parsopercularis	46	0.07	0.72	0.53	0.598	1.32	1.57	4.53	**0.000**	−0.13	1.11	−0.49	0.632
Lh parsorbitalis	47	−0.30	1.75	−1.00	0.326	0.51	2.63	1.05	0.304	−0.43	1.51	−1.19	0.249
Lh parstriangularis	48	0.21	1.16	1.05	0.303	1.27	2.21	3.09	**0.004**	−0.17	1.59	−0.46	0.653
Lh pericalcarine	49	0.32	0.71	2.56	0.015	0.55	0.96	3.07	**0.005**	0.39	0.99	1.65	0.117
Lh postcentral	50	−0.03	0.97	−0.17	0.869	0.81	1.52	2.89	**0.007**	−0.17	1.74	−0.43	0.675
Lh posterior cingulate	51	0.15	0.78	1.13	0.267	0.78	1.02	4.13	**0.000**	0.28	0.75	1.60	0.128
Lh precentral	52	0.05	0.56	0.53	0.600	1.01	1.31	4.17	**0.000**	0.05	1.44	0.14	0.893
Lh precuneus	53	0.11	0.51	1.22	0.232	0.81	0.77	5.65	**0.000**	0.04	0.81	0.19	0.849
Lh rostral anterior cingulate	54	0.19	0.83	1.35	0.186	0.73	1.17	3.39	**0.002**	−0.10	1.20	−0.35	0.732
Lh rostral middle frontal	55	0.14	0.96	0.87	0.391	0.93	1.61	3.12	**0.004**	−0.08	1.30	−0.27	0.793
Lh superior frontal	56	0.06	0.94	0.34	0.737	1.09	1.56	3.77	**0.001**	0.15	0.97	0.67	0.509
Lh superior parietal	57	−0.04	0.65	−0.37	0.713	0.69	1.06	3.54	**0.001**	−0.20	1.32	−0.63	0.538
Lh superior temporal	58	0.23	1.13	1.16	0.256	1.10	1.70	3.47	**0.002**	0.01	0.94	0.04	0.970
Lh supramarginal	59	0.14	1.04	0.76	0.452	1.14	1.48	4.15	**0.000**	−0.12	1.48	−0.34	0.738
Lh frontal pole	60	−0.29	1.64	−1.01	0.318	0.18	2.89	0.34	0.736	−0.49	1.56	−1.32	0.203
Lh temporal pole	61	−0.02	2.34	−0.04	0.967	1.99	3.03	3.53	**0.001**	0.21	2.17	0.40	0.691
Lh transverse temporal	62	0.47	0.93	2.89	0.007	0.90	1.61	2.99	**0.006**	0.30	1.51	0.86	0.404
Lh insula	63	0.12	0.77	0.93	0.360	1.46	1.39	5.65	**0.000**	0.16	0.96	0.68	0.509
Rh banks sts	64	0.82	0.98	4.80	**0.000**	1.61	1.67	5.18	**0.000**	−0.21	1.13	−0.79	0.443
Rh caudal anterior cingulate	65	−0.04	1.01	−0.23	0.817	1.91	1.45	7.07	**0.000**	0.05	1.48	0.15	0.880
Rh caudal middle frontal	66	0.07	0.79	0.49	0.626	1.00	1.13	4.78	**0.000**	0.20	2.00	0.42	0.677
Rh cuneus	67	0.28	0.68	2.35	0.025	0.48	0.88	2.93	**0.007**	0.10	0.66	0.67	0.512
Rh entorhinal	68	−0.19	1.49	−0.73	0.470	2.94	3.14	5.05	**0.000**	1.32	2.11	2.66	0.017

Table 2 (*continued*)

ROI		T2 (N = 33)				T3 (N = 29)				T4 (N = 18)			
		Volume change (%)		One-sample *t*-test		Volume change (%)		One-sample *t*-test		Volume change (%)		One-sample *t*-test	
	#	Mean	SD	t	p	Mean	SD	t	p	Mean	SD	t	p
Rh fusiform	69	0.21	0.63	1.93	0.063	1.51	1.29	6.30	**0.000**	0.10	1.02	0.43	0.673
Rh inferior parietal	70	0.38	0.84	2.57	0.015	1.07	1.27	4.51	**0.000**	−0.17	1.18	−0.61	0.550
Rh inferior temporal	71	0.28	0.63	2.57	0.015	1.70	1.40	6.53	**0.000**	−0.08	1.25	−0.27	0.791
Rh isthmus cingulate	72	0.29	0.83	2.02	0.052	0.36	0.97	1.99	0.056	0.13	0.99	0.55	0.587
Rh lateral occipital	73	0.41	0.66	3.63	**0.001**	0.97	0.99	5.30	**0.000**	−0.02	0.97	−0.09	0.929
Rh lateral orbitofrontal	74	0.28	1.21	1.32	0.196	1.05	1.50	3.78	**0.001**	0.37	1.38	1.13	0.275
Rh lingual	75	0.37	0.65	3.25	**0.003**	0.77	0.95	4.36	**0.000**	0.15	0.69	0.93	0.368
Rh medial orbitofrontal	76	0.20	0.73	1.60	0.120	0.89	1.32	3.63	**0.001**	0.17	1.10	0.65	0.527
Rh middle temporal	77	0.56	1.00	3.19	**0.003**	1.56	1.69	4.97	**0.000**	−0.20	1.44	−0.61	0.553
Rh parahippocampal	78	−0.07	1.03	−0.41	0.687	2.06	1.77	6.26	**0.000**	0.36	1.17	1.29	0.214
Rh paracentral	79	0.10	0.70	0.85	0.404	1.08	1.22	4.75	**0.000**	0.06	1.14	0.21	0.835
Rh parsopercularis	80	0.16	0.73	1.23	0.228	1.11	1.58	3.78	**0.001**	−0.10	1.08	−0.39	0.705
Rh parsorbitalis	81	−0.17	1.48	−0.65	0.518	0.98	2.13	2.49	**0.019**	0.06	1.48	0.16	0.873
Rh parstriangularis	82	0.43	1.06	2.36	0.025	1.09	1.81	3.24	**0.003**	−0.06	1.69	−0.15	0.885
Rh pericalcarine	83	0.34	0.85	2.31	0.028	0.31	1.01	1.65	0.111	0.08	0.90	0.37	0.717
Rh postcentral	84	0.18	0.67	1.54	0.134	0.94	1.03	4.90	**0.000**	−0.06	1.18	−0.21	0.834
Rh posterior cingulate	85	0.13	0.69	1.07	0.294	0.72	1.21	3.21	**0.003**	0.17	1.23	0.60	0.554
Rh precentral	86	0.14	0.67	1.19	0.241	0.98	1.36	3.88	**0.001**	0.01	1.49	0.04	0.972
Rh precuneus	87	0.03	0.53	0.35	0.731	0.73	0.83	4.75	**0.000**	−0.05	0.97	−0.21	0.839
Rh rostral anterior cingulate	88	0.26	0.73	2.07	0.047	1.78	1.48	6.48	**0.000**	−0.02	1.22	−0.08	0.937
Rh rostral middle frontal	89	0.35	1.03	1.93	0.062	0.99	1.73	3.07	**0.005**	−0.05	1.48	−0.13	0.898
Rh superior frontal	90	0.04	0.90	0.25	0.808	1.16	1.71	3.66	**0.001**	0.16	1.65	0.42	0.678
Rh superior parietal	91	−0.04	0.63	−0.35	0.729	0.76	1.04	3.94	**0.000**	−0.17	1.12	−0.64	0.530
Rh superior temporal	92	0.41	0.84	2.84	0.008	2.27	1.68	7.28	**0.000**	0.19	1.31	0.63	0.539
Rh supramarginal	93	0.28	0.91	1.76	0.089	1.41	1.60	4.75	**0.000**	0.17	1.22	0.61	0.550
Rh frontal pole	94	−0.34	2.17	−0.89	0.379	1.01	3.28	1.66	0.108	−0.28	2.20	−0.54	0.599
Rh temporal pole	95	0.20	2.05	0.56	0.577	4.13	2.84	7.85	**0.000**	1.40	2.35	2.54	0.021
Rh transverse temporal	96	0.35	1.01	1.97	0.057	1.30	1.43	4.89	**0.000**	0.06	1.13	0.23	0.822
Rh insula	97	0.05	0.77	0.37	0.711	2.50	1.46	9.24	**0.000**	0.10	1.25	0.34	0.737

and parahippocampal cortices, fusiform, lingual and paracentral gyri and the insula. Finally, after six months from the end of the treatment (T4), the right amygdala volume increase observed in patients having received ECT was significantly more pronounced than changes observed in HC (mean difference = 1.91, t = 3.45, p = 0.002).

3.4. Association between volume changes at successive timepoints

Volume changes at the end of the ECT series (T3) were significantly positively predicted by volume changes after the first treatment (T2) in some cortical regions, namely in the temporal pole and superior frontal gyrus bilaterally, in caudal middle frontal gyrus, pars orbitalis and triangularis of the inferior frontal gyrus, precentral and postcentral gyri, supramarginal gyrus, and entorhinal cortex in the left hemisphere, in frontal pole, lateral orbitofrontal cortex and rostral middle frontal gyrus in the right hemisphere, both according to unadjusted and adjusted linear model controlling for the number of ECT sessions ($p_{FDR} < 0.05$) (Supplementary Table 3). However, when including among predictors an interaction between volume changes at T2 and number of sessions, no significant predictors of volume changes at T3 were found. Number of ECT sessions were not found to predict volume changes after the end of treatment (T3) in any model.

Volumetric changes after six months from the end of the treatment (T4) were significantly positively predicted by volume changes at T3 in several cortical and subcortical ROIs ($p_{FDR} < 0.05$) (Supplementary Table 3). In the cortex, changes at T3 and T4 were significantly correlated bilaterally in the frontal pole, superior frontal gyrus, the three parts of the inferior frontal gyrus, precentral and postcentral gyri, superior parietal gyrus, superior, middle and transverse temporal gyri, insula, parahippocampal cortex, posterior cingulate cortex and precuneus; on the left side in the temporal pole, inferior temporal gyrus, lateral occipital and pericalcarine cortex; on the right side in rostral middle frontal gyrus, medial orbitofrontal cortex, paracentral cortex, rostral and caudal anterior cingulate cortex. In addition, volume changes were significantly positively correlated bilaterally in the putamen, amygdala and ventral diencephalon, cerebral white matter, lateral ventricles and fourth ventricle, but also in the left pallidum and left cerebellum cortex and in the right thalamus proper.

3.5. Cross-sectional comparisons

Before the first treatment (T1), depressed patients showed significantly smaller volumes than HC in the left parahippocampal cortex ($p_{FDR} < 0.05$). After the first treatment (T2), significant differences were still found in the same region, while differences between patients and HC in left parahippocampal cortex detected at the end of the treatment (T3) and after six months (T4) did not survived correction for multiple comparisons (Supplementary Table 4).

3.6. Exploratory associations with clinical scores

None of the significant treatment-related volume changes observed at T2 were found to predict depression severity decrease at the end of the treatment ($MADRS_{T3\text{-}T1}$), EMQ change and AMI-SF consistency at T3. Significant correlations between volume changes and clinical scores at the end of treatment (T3) were found instead (Supplementary Table 5). None of these results were corrected for multiple testing.

Table 3
Comparisons of volume changes among ECT patients, HC and ECV patients at T2, and between ECT patients and HC at T3. Only significant pairwise mean differences between groups are shown, based on Tukey's post-hoc test at T2 and two-sample *t*-test at T3. *Abbreviations: ROI = region of interest; SD = standard deviation; L = left; R = right; Lh = left cortical hemisphere; Rh = right cortical hemisphere; NS = not significant.*

	T2: 33 ECT vs. 18 HC vs. 16 ECV		Mean differences	
ROI	F	p	ECT - HC	ECT - ECV
L thalamus proper	3.90	0.024	0.40	NS
L hippocampus	5.50	0.006	NS	1.10
R putamen	4.60	0.013	NS	0.50
R hippocampus	2.40	0.098	NS	NS
brain stem	6.70	0.002	0.40	0.40
R inf lat vent	6.30	0.003	2.70	3.40
Rh banks sts	5.80	0.005	0.90	0.80
Rh lateral occipital	4.40	0.017	0.40	NS
Rh lingual	2.90	0.064	NS	NS
Rh middle temporal	4.60	0.013	0.70	NS
	T3: 29 ECT vs. 16 HC		**Mean differences**	
ROI	**t**	**p**	**ECT - HC**	**ECT - ECV**
L thalamus proper	4.52	0.000	0.94	-
L caudate	3.26	0.002	1.18	-
L putamen	3.02	0.004	0.66	-
L pallidum	1.82	0.078	NS	-
L hippocampus	4.79	0.000	1.93	-
L amygdala	4.30	0.000	2.35	-
L accumbens area	2.54	0.015	1.20	-
R thalamus proper	4.74	0.000	1.20	-
R caudate	3.33	0.002	1.05	-
R putamen	6.89	0.000	1.59	-
R pallidum	3.25	0.002	0.75	-
R hippocampus	7.89	0.000	3.20	-
R amygdala	9.19	0.000	6.08	-
R accumbens area	3.39	0.002	1.93	-
R ventraldc	3.33	0.002	0.74	-
L lateral ventricle	−2.22	0.032	−3.84	-
L inf lat vent	−1.68	0.100	NS	-
3rd ventricle	−3.34	0.002	−6.10	-
R lateral ventricle	−3.14	0.003	−5.03	-
R inf lat vent	−2.18	0.036	−5.28	-
Lh banks sts	0.73	0.469	NS	-
Lh caudal anterior cingulate	4.84	0.000	1.77	-
Lh caudal middle frontal	0.85	0.402	NS	-
Lh cuneus	2.12	0.040	0.40	-
Lh entorhinal	2.51	0.016	1.47	-
Lh fusiform	3.16	0.003	0.84	-
Lh inferior parietal	0.89	0.382	NS	-
Lh inferior temporal	1.18	0.246	NS	-
Lh isthmus cingulate	1.73	0.092	NS	-
Lh lateral occipital	1.26	0.218	NS	-
Lh lingual	2.74	0.009	0.48	-
Lh middle temporal	0.19	0.849	NS	-
Lh parahippocampal	2.40	0.022	0.93	-
Lh paracentral	4.10	0.000	1.15	-
Lh pars opercularis	1.39	0.176	NS	-
Lh pars triangularis	0.98	0.334	NS	-
Lh pericalcarine	1.66	0.104	NS	-
Lh postcentral	0.50	0.619	NS	-
Lh posterior cingulate	2.72	0.009	0.69	-
Lh precentral	0.99	0.331	NS	-
Lh precuneus	2.80	0.009	0.70	-
Lh rostral anterior cingulate	0.99	0.329	NS	-
Lh rostral middle frontal	0.53	0.602	NS	-
Lh superior frontal	0.92	0.367	NS	-
Lh superior parietal	0.94	0.359	NS	-
Lh superior temporal	0.75	0.460	NS	-
Lh supra marginal	0.01	0.995	NS	-
Lh temporal pole	1.33	0.194	NS	-
Lh transverse temporal	1.90	0.065	NS	-
Lh insula	3.24	0.002	1.21	-
Rh banks sts	3.05	0.004	1.46	-
Rh caudal anterior cingulate	3.97	0.000	1.79	-
Rh caudal middle frontal	0.79	0.438	NS	-
Rh cuneus	1.57	0.124	NS	-
Rh entorhinal	3.97	0.000	2.86	-
Rh fusiform	4.11	0.000	1.25	-
Rh inferior parietal	1.41	0.169	NS	-
Rh inferior temporal	4.39	0.000	1.58	-
Rh lateral occipital	3.64	0.001	0.79	-
Rh lateral orbitofrontal	3.33	0.002	1.21	-
Rh lingual	3.39	0.002	0.74	-
Rh medial orbitofrontal	2.09	0.044	0.78	-
Rh middle temporal	2.60	0.014	1.44	-
Rh parahippocampal	4.68	0.000	2.04	-
Rh paracentral	3.09	0.004	1.09	-
Rh pars opercularis	1.90	0.065	NS	-
Rh pars orbitalis	1.08	0.290	NS	-
Rh pars triangularis	1.37	0.182	NS	-
Rh postcentral	2.26	0.031	0.78	-
Rh posterior cingulate	2.35	0.024	0.75	-
Rh precentral	1.44	0.161	NS	-
Rh precuneus	2.34	0.027	0.67	-
Rh rostral anterior cingulate	3.34	0.002	1.59	-
Rh rostral middle frontal	0.62	0.543	NS	-
Rh superior frontal	1.43	0.163	NS	-
Rh superior parietal	1.33	0.193	NS	-
Rh superior temporal	4.28	0.000	2.20	-
Rh supra marginal	1.82	0.082	NS	-
Rh temporal pole	3.36	0.002	3.07	-
Rh transverse temporal	4.24	0.000	1.44	-
Rh insula	7.89	0.000	2.57	-

Volume increases in left amygdala at T3 were positively correlated with $MADRS_{T3\text{-}T1}$ ($B = 2.94$, $p = 0.003$) also when adjusting for the number of ECT sessions ($B = 2.93$, $p = 0.004$); i.e. the greater the volume increase, the lesser the decrease in depression severity. Volume increase in left caudal anterior cingulate cortex was also significantly positively associated with $MADRS_{T3\text{-}T1}$, but only when not adjusting for the number of sessions ($B = 3.82$, $p = 0.041$). Right lateral and medial orbitofrontal cortex volume increases were negatively correlated with $EMQ_{T3\text{-}T1}$ ($B = -14.78$, $p = 0.013$; $B = -11.79$, $p = 0.040$), also when adjusting for the number of treatments ($B = -14.75$, $p = 0.016$; $B = -11.74$, $p = 0.047$); i.e. the greater the increase, the greater the reduction of subjective memory complaints. In addition, only when adjusting for the number of ECTs, left superior parietal gyrus volume increase was found to be positively correlated with AMI-SF consistency at T3 ($B = 6.11$, $p = 0.037$); i.e. the greater the volume increase, the higher the consistency in autobiographical memory. Finally, volume increases in right thalamus proper ($B = 0.12$, $p = 0.024$), left paracentral gyrus ($B = 0.13$, $p = 0.020$) and right postcentral gyrus ($B = 0.11$, $p = 0.021$) were significantly positively predicted by the number of treatments, while a negative association was found with volume change in right inferior lateral ventricle ($B = -1.24$, $p = 0.026$). No significant associations between right amygdala volume increase and clinical scores at T4 were detected (Supplementary Table 5).

4. Discussion

To the best of our knowledge, this is the first study investigating immediate volumetric effects of ECT. A trend toward volume increase was already observable in most regions after approximately 2 h from the first ECT session, with significant results in the brain stem, the bilateral hippocampi, right putamen and left thalamus and temporal and occipital regions in the right hemisphere. As far as we know, increased hippocampus and amygdala volumes have previously been reported after the second ECT session [20], but no

study has investigated the immediate effects of a single ECT session. Such changes were not observed in HC, nor in patients receiving anesthesia for ECV. Notably, the immediate effects of ECT were significantly correlated with volume changes after the end of treatment only in a few cortical regions of interest, and no significant interactions with number of ECT sessions were detected, thus a linear cumulative process of the immediate effects seems unlikely as the underlying mechanism for volume increases induced by the ECT series. Indeed, for ROIs representing the cerebral ventricles, the volume changes at T2 and T3 were opposite, while no changes in subcortical regions after ECT were predicted by immediate effects.

Moreover, it is noteworthy that, among others, volumetric increases in the brain stem were significantly more pronounced in ECT patients in comparison with both HC and ECV patients, thus being probably independent from time-of-day effects and anesthesia effects. Importantly, brain stem changes were transient and could not be observed at later timepoints. They may be related to the mechanisms underlying generalized seizure induction given the role of the reticular formation in tonic-clonic seizures generation [36,37], but also to the enhancement of serotonergic and dopaminergic neurotransmission observed after ECS/ECT [8].

Other studies have examined short-term changes in T1 and T2 relaxation time to clarify whether ECT could induce a breakdown in the blood-brain barrier and subsequent changes in brain water content, variably interpreted as edema and/or increased blood flow. Mander and colleagues were the first to observe an increase in T1 relaxation time of a brain transverse section within 1 h after the first and last ECT session [38]. Significant transient increases in T1 relaxation time were later confirmed in non-dominant cerebral hemisphere both 25 min and 2 h after ECT [39]. A non-significant rise in T2 relaxation time was also observed, reaching its maximum at 2 h after ECT [39]. Increased T2 relaxation time were also reported in medial temporal lobes and thalamus approximately 2-2½ hours after ECT, with significant differences in the thalami between 1 and 2 days before the first session and 2-2½ hours after the second one [40]. However, more recent studies by Girish et al. failed to replicate increases in T2 relaxation time measured bilaterally in thalamus, hippocampus, medial temporal lobes and dorsolateral frontal cortex one day before the first ECT and 2 h after the second session [41,42]. Given the inconsistency of previous results and the small sample sizes, no conclusions could be drawn to infer a role of increased water content in the volumetric increases observed in our study 2 h after ECT. Interestingly, in a subgroup of patients included in this study, we observed an increase in isotropic hindered diffusion in white matter extra-neurite water compartment 2 h after the first ECT, which could stem from an increase in water content [43]. A localized vasogenic edema could be excluded, at least in the hippocampus, where a decrease in mean diffusivity has been repeatedly observed [44–46], at later stages of treatment (i.e. observed within one week from the end of ECT series).

More consistent results have been obtained from animal studies on ECS. Indeed, neurogenesis, gliogenesis and angiogenesis demonstrated in rats receiving both acute and chronic ECS, have been proposed to underlie the volumetric increases observed in patients treated with ECT [12]. However, the possibility of neuroplasticity underlying the immediate volumetric effects observed in our study seems implausible. In the first report on ECS-induced neurogenesis in the dentate gyrus of rats, maximal cell proliferation seemed to occur on days 3 and 5 after the administration of a single ECS, without increases in the first 12 h [13]. The seizure-induced proliferation of neural progenitors in dentate gyrus also overlaps in time with that of glial progenitors [14]. Endothelial and neural proliferation in the dentate gyrus have also been shown to occur in concert, with significant increase in endothelial cells proliferation on the second day after a single ECS, but not at day 0, 4, 6 or 8, and increased number of proliferating cluster (endothelial plus neural) cells in the subgranular zone at days 2 through 6, peaking at day 4 [15]. Conversely, transient morphological changes associated with glial cells activation have been shown to occur as early as 2 h after the last of a series of ECS, with microglial cells, astrocytes and NG2-positive glial cells showing thicker and slightly shortened processes and larger cell bodies [47]. However, even though changes in glial number and morphology, together with axon sprouting, dendritic branching and synaptogenesis, have been proposed as cellular events underlying gray matter changes detected by MRI [48], studies are needed in order to elucidate the relationship between micro- and macrostructural events, especially in such a limited timeframe. Indeed, glial activation, cerebral edema and blood-brain barrier permeability changes are likely to co-occur and have been repeatedly observed after inflammatory acute insults originated outside the brain [49]. The short-term volumetric effects observed in our study could thus also be interpreted in light of the hypothesis proposed by Van Buel and colleagues, which posits that inflammatory response, mainly induced in the periphery minutes to hours after single ECT sessions, could mobilize neurotrophin expression and endogenous neuroprotection [11].

Neuroinflammation is less likely to explain the volume changes observed at 6 months. In particular, the right amygdala volume increase was still significant and most cortical and subcortical volumes were still increased, including in the left amygdala and temporal cortical regions. Interestingly, volume increase after 7–14 days from the last ECT session was more pronounced in the right amygdala, which also showed the greatest (and the only significant) increase after 6 months. On the other hand, in many regions, the greater changes after 6 months were observed in patients with greater changes at the end of the ECT series, suggesting the possibility of durable influences on brain structure. In animal models, newborn cells after a single ECS were found to differentiate and survive for at least 3 months and the number of neurons formed was positively correlated with the number of ECS trials administered [13], resembling the relationship observed between response probability and number of treatments in humans [50]. Increased gray matter volumes in the long-term could thus be explained by the neurotrophic effects which would underlie volume increases at the end of the treatment course. Long-term changes in gray matter volumes after ECT have also been recently reported in temporal regions by Gyger and colleagues [51]. Nonetheless, our findings should be considered preliminary and warrant replication from other samples or multi-site investigations. Even though a correction for multiple comparisons was applied to longitudinal analyses to reduce the risk of false positive error, the small sample size and the high number of ROIs still suggest caution in interpreting these results.

Surprisingly, after the end of ECT treatment, volume increases in the amygdala and in the anterior cingulate cortex were negatively associated with depression outcome, with a greater increase in volume corresponding to a lesser decrease in depression severity. However, these findings seem questionable in light of the null correlations between volume change and ECT outcome observed in the more powered GEMRIC study [18]. Similarly, some exploratory associations between volume increases after the ECT course and changes in subjective memory complaints or autobiographical memory consistency were observed, respectively in the right orbitofrontal cortex and in the left superior parietal gyrus, which, if replicated, could warrant some more attention. However, given the high number of models tested and the uncorrected level of significance, also these findings should be interpreted with caution. Indeed, despite recent findings of a significant association between hippocampal volume change and cognitive impairments [52,53],

no relationship between hippocampal volume increase and subjective and autobiographic memory measures was observed in our study.

Some other limitations should be acknowledged. The samples were not perfectly matched in terms of gender, age and time of scan. In comparison with ECT patients, HC were more frequently females and ECV patients were mostly male. These latter were also older in comparison with ECT patients and were scanned at different times. Unfortunately, the anesthetic used was different between ECT and ECV patients. However, our main analysis was focused on changes within subjects, and we controlled for age and gender in cross-sectional comparisons.

5. Conclusions

In our study, we evaluated the timing of volume changes induced in cortical and subcortical regions by ECT in depressed patients scanned 2 h before and after their first ECT session, 7–14 days after the end of the ECT series and at 6 months follow-up. As expected based on the recent GEMRIC results [18], widespread volume increases were observed in both cortical and subcortical areas after the whole course of ECT. More interestingly, volume increases were also observed approximately 2 h after the first ECT – excluding neurogenesis as the underlying mechanism. Furthermore, volume increase remained in the amygdala 6 months after the end of treatment, implying that different biological mechanisms could be in play at different time points. In future human and animal studies focusing on brain micro- and macrostructural changes induced by ECT, more attention should be given to the timing of changes observed and different approaches should be encouraged to elucidate the relationship between molecular and cellular processes and their morphological correlates.

Funding

The work was supported by Western Norway Regional Health Authority Grant Nos. 911986 and 912238.

CRediT authorship contribution statement

Giulio Emilio Brancati: Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Njål Brekke:** Software, Data curation, Writing – review & editing. **Hauke Bartsch:** Software, Data curation, Writing – review & editing, All authors critically revised the manuscript for important intellectual content and read and approved the final version. **Ole Johan Evjenth Sørhaug:** Data curation, Writing – review & editing. **Olga Therese Ousdal:** Data curation, Writing – review & editing. **Åsa Hammar:** Conceptualization, Investigation, Writing – review & editing. **Peter Moritz Schuster:** Investigation, Writing – review & editing. **Ketil Joachim Oedegaard:** Conceptualization, Resources, Writing – review & editing, Project administration, Funding acquisition. **Ute Kessler:** Conceptualization, Investigation, Resources, Writing – review & editing, Data curation, Project administration. **Leif Oltedal:** Conceptualization, Investigation, Methodology, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Acknowledgements

We are thankful to Vera Jane Erchinger and Leila Marie Frid for contributions to participant inclusion and study logistics. We also thank all study participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.08.018.

Author's contributions

GEB performed analysis and wrote the manuscript. LO supervised the study. UK, LO, KJO and ÅH contributed to the design and study planning. UK, PMS, OJE, HB, LO, NB, OTO contributed to data collection/processing/analysis. All authors critically revised the manuscript for important intellectual content and read and approved the final version.

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