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Electroconvulsive therapy induced gray matter increase is not necessarily correlated with clinical data in depressed patients

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ABSTRACT

Background: Electroconvulsive therapy (ECT) and depression have been associated with brain volume changes, especially in the hippocampus and the amygdala.
Methods: In this retrospective study we collected data from individual pre-post ECT whole brain magnetic resonance imaging scans of depressed patients from six German university hospitals. Gray matter volume (GMV) changes were quantified via voxel-based morphometry in a total sample of 92 patients with major depressive episodes (MDE). Additionally, 43 healthy controls were scanned twice within a similar time interval.
Results: Most prominently longitudinal GMV increases occurred in temporal lobe regions. Within specific region of interests we detected significant increases of GMV in the hippocampus and the amygdala. These results were more pronounced in the right hemisphere. Decreases in GMV were not observed. GMV changes did not correlate with psychopathology, age, gender or number of ECT sessions. We ruled out white matter reductions as a possible indirect cause of the detected GMV increase.
Conclusion: The present findings support the notion of hippocampus and amygdala modulation following an acute ECT series in patients with MDE. These results corroborate the hypothesis that ECT enables primarily unspecific and regionally dependent neuroplasticity effects to the brain.

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Introduction

Depression remains a highly prevalent illness with an enormous individual and societal burden. Electroconvulsive therapy (ECT) is a treatment of choice for severe, drug-resistant or psychotic depressive episodes [1] and national treatment guidelines in Germany follow these recommendations [2].

According to the neurotrophic hypothesis of depression [3] changes in neuroplasticity or even in morphometry can be expected. Indeed, smaller hippocampi especially in chronically depressed patients have been reported for more than two decades [4]. The first confirmative meta-analyses were presented in 2004 [5,6]. Later on, evidence was reported for hippocampal atrophy as a state marker, correlating with the length and number of depressive episodes [7]. Additionally, it has been shown that pharmacotherapy provided a protective effect in a volumetric study of 30 patients compared to 30 healthy controls [8].

The exact mechanism of action of ECT remains unclear so far. However it is widely accepted that ECT induces neuroplastic changes, which are related to the mechanisms of action of ECT [9–11]. These findings mirror the neurotrophic hypothesis of depression [3,12,13]. Nevertheless, it seems plausible that ECT primarily exerts regionally and biologically specific, but clinically unspecific effects on the brain. This hypothesis might be supported by ECT's curative effects on a number of psychopathological syndromes and conditions besides depression like psychosis [14], catatonia [15], mania [16,17], delirium [18,19], parkinsonism [20], suicidality [21], autoaggression [22] and agitation [23,24].

Nordanskog et al. were the first to report on volume increases of specific brain regions like the hippocampus following an ECT treatment [25]. The latest meta-analysis demonstrated a hippocampal volume increase in 174 patients included from 9 studies [26]. Interestingly, within this analysis no correlation was found between the growth and the improvement of symptoms, concomitant medication, age, gender, bipolarity, number of ECTs or electrode position. Thus, effect sizes of cofactors leading to hippocampal volume increase might be small or, on the other hand, may indicate unspecific contributions to ECT mechanisms of action. Two studies have shown hippocampal gray matter increase that covaried with symptom alleviation so far [27,28]. In this context it is important to take a closer look at the time-course of the described volume changes over a longer time period: The only existing follow-up study found that the hippocampal volume increase vanished after several months [29].

Quite less evidence exists for an ECT induced volume increase of the amygdala [30]. It has to be emphasized that so far, the amygdala has not been associated to the clinical outcome of ECT.

To address the problem of a possible confounding influence of basic clinical conditions on hippocampal gray matter volume (GMV) increase, we collected raw data from 92 patients from six German university hospitals, who received ECT as treatment of a major depressive episode. All of them had a high-resolution magnetic resonance scan, each pre and post treatment, to detect changes in GMV.

Aims of the study

Due to the above mentioned syndromic unspecificity of ECT, we hypothesized to find volume increases but a lack of correlation to clinical data in depressed patients following an ECT treatment. It has to be emphasized that ECT-induced unspecific, but still regionally restricted volume increase can very well reflect a necessary precondition for a successful therapy of treatment resistant depression.

Beyond hippocampus and amygdala as regions of interest we hypothesized a pre post ECT increase of gray matter volume within the habenula, since post mortem evidence [31] and high-resolution magnetic resonance imaging studies [32,33] indicated lower habenula gray matter volume in patients with depression. In addition, habenula deep brain stimulation clinical findings [34,35] suggested such changes.

Materials and methods

Subjects

Ninety-two inpatients from six different sites (Aachen, Göttingen, Heidelberg, Mannheim, Marburg, Münster) fulfilling the diagnostic criteria of a major depressive episode (MDE), as defined by the Diagnostic and Statistical Manual, 4th edition (DSM-IV-TR) were enrolled into this analysis. Additionally, 43 healthy controls (HC) were scanned twice. HC were recruited through public notices and newspaper announcements in Aachen and Münster. Scanning procedures were identical to patients at both sites. Time interval was exactly 8 weeks for all HCs in Aachen and mean = 38.44 days, SD = 9.72 in Münster.

Partly, data of local patient groups have been published before (e.g. from Mannheim [32,36,37], Aachen [38], Münster [39] and Heidelberg [40]).

All subjects gave written, informed consent before enrollment at local study centers. The analysis and all underlying studies were approved by each of the local ethics committees in accordance with the Declaration of Helsinki.

Remission was defined as a post ECT HAMD score below 10 [41]. Response was defined as a decrease of the initial HAMD score greater than 50%.

ECT

Altogether, 12 subjects received bilateral ECT, while 69 were treated with a right unilateral electrode position. All other patients had different electrode positions (n = 3) or a switch in electrode position (n = 8).

All centers used a Thymatron IV ECT device (Somatics, LLC. Lake Bluff, IL, USA).

Further details on ECT parameters are summarized in Supplementary Table 1.

MR image acquisition

All MR scans were acquired within 2 weeks before the first and two weeks after the last ECT (or less), and all were acquired with 3T MRI scanners.

Details on MR image acquisition and timing are summarized in Supplementary Table 2.

MR image analysis

All preprocessing steps and statistical analysis of the MRI data were carried out using the SPM12 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

Longitudinal comparison

At first, pre and post ECT T1-weighted anatomical images of the patients were coregistered by aligning the later acquired image to the earlier image via a rigid body transformation (SPM12 coregister) to minimize the differences between the images caused by the positioning of the individuals within the head coil.

The next step was the registration of the later image to the earlier image using the longitudinal registration toolbox of SPM12 including a bias correction [42]. This longitudinal registration tool, a substitute of the high dimensional warp tool of SPM8, constructs an average or midpoint image and warps the individual images to this average to maximize the spatial conformity. Each warp process results in a deformation matrix, which reflects the change necessary for fitting the individual image to the midpoint image, voxel by voxel. The Jacobian determinant which maps these necessary deformations is produced for each participant and represents the degree of contraction or expansion that is required to transform a given voxel from the respective scan to the same voxel space of the midpoint image. The saved Jacobian rate is the difference between the two Jacobian determinants.

Midpoint images were further processed using the segment routine of SPM12 using 6 different tissue probability maps. Native segmented images as well as DARTEL imported images were saved. The resulting native gray matter images were multiplied with the Jacobian rate resulting in an image reflecting the morphometric changes between the two time points within the gray matter. To minimize the possibility of including white matter and other areas outside of gray matter and to avoid edge effects the value of the minimal amount of gray matter was set at 20% (0.2 voxel value) [43,44].

The resulting "Jacobian difference" images were normalized and smoothed with a 8 mm kernel (see also – template section).

Template and normalization

For normalization of the segmented images the DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra) approach [45] was used to enable a more accurate spatial normalization. All native (rc1_01,r c1_02, rc2_01,rc2_02; rc1avg) DARTEL imported images of each patient and healthy control (HC) were normalized to an "existing template", more precisely to the IXI550 template. The resulting flow fields were used to normalize the native gray and white matter images into MNI space. For images representing the Jacobian difference and therefore the longitudinal change unmodulated images were saved, using the "preserve concentration" option. Images of the single time points were used as modulated images, preserving the "amount" to use the volume information.

For this process the IXI550 template of the VBM8 toolbox was used, due to the fact that all 6 versions of a template of 550 subjects created with DARTEL are provided. This was done to avoid a "bias" of the sample. The different comparisons and regression analysis were performed with different samples (depending on the available data), so one customized template would inherit the bias of the selection. The voxel size was harmonized to $1 \times 1 \times 1$ mm.

To avoid segmentation faults, the clean-up routine of the segmentation tool that extracts brain from the segmented images was set to "thorough clean" additionally the option for bias correction was used to refer to field inhomogeneity.

All normalized images were smoothed with an 8 mm isotropic Gaussian kernel.

Whole brain GMV changes represented by the Jacobian rate images were entered in several multiple regression analyses with age and sex and site as covariates of no interest.

To verify the result of the whole brain analysis and confirm that it is not caused by a bias due to white matter reduction, we extracted the mean voxel values of the hippocampus and other brain regions for gray and white matter for both time-points. To assess the local volume changes of the hippocampal formation the volume of the hippocampus and the amygdala was estimated via the integration of all gray matter voxels within the respective mask.

Masks for regions of interest (ROI), hippocampus, amygdala and thalamus, were created using the WFU PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas). To extract the voxel values of the habenula, we created a 2 mm sphere around the coordinates reported by Ullsperger [48] (L/R Habenular complex (bilateral) x = 3/-5 y = −25 z = 8 (Talairach) transferred into MNI space (5,-24,6; −5,-26,8)).

An integration of all voxels of the native tissue class images in spatial correspondence to the original data was used to estimate the whole brain volume [46,47]. This revealed measures of global GM, WM and CSF compartment volumes for each participant, the sum of all three compartments served as an estimate of total intracranial volume (TIV).

To express the whole brain GM volume changed, we computed the change in GM to TIV volume between the time points in percent.

The extracted GM and WM voxel values as well as the estimated GM volume for the regions of interest were used to analyze regional changes.

Statistical analysis

The approach for the statistical analysis depended on the nature of the data.

The analysis of the regional volume change (Jacobian difference image) was performed with SPM12. To determine the volume increase on the whole brain level we performed a one-sample *t*-test on those images representing the longitudinal change within one subject. The results represent those brain regions where the majority of the patients showed a change which is interpreted as volume increase. Age and sex were included as covariates in this analysis.

To test the correlation of the change to clinical variables whole brain regression analyses with the computed percentages of changes in HAMD scale, MMSE and number of ECTs as independent variables were performed with SPM12. Age and sex were used as covariates of no interest for these analyses.

Results concerning the whole brain GM volume change (Jacobian difference image) are reported with a threshold of $p = 0.05$ family wise error (FWE) whole brain corrected at the voxel level.

The analysis of the local changes, represented by the estimated GM volume and the mean voxel values of gray and white matter within a region of interest were accomplished with IBM SPSS statistics 23. The threshold for significance in these analyses was set to 0.05.

We performed linear mixed model analyses with time as the repeated factor and diagnosis as fixed factor. Age and sex and site were included as covariates and co-factors, respectively.

The threshold for significance in these analyses was set to 0.05.

Results

Demographics

Forty-two of the 92 patients were female; mean age was 50 y ± 12 y (see Table 1). Age of the included patients differed between the sites ($F = 3.2$ $df = 5$, $p = 0.01$), with Aachen providing the oldest sample (mean = 58 y) and Münster and Heidelberg the youngest patients (mean = 46 y).

Patients were screened using the Hamilton Depression Scale (HAMD, 21 item version) (n = 92, pre ECT 26.1 ± 7; post ECT 11.4 ± 7.4) and the Mini-Mental-Status-Examination (MMSE) (pre ECT 27.9 ± 1.9; post ECT 27.9 ± 3.5, data only from = 39 to 37 patients, respectively). Differences between sites were significant ($F = 5.5$, $df = 5$, $p < 0.001$), with Mannheim entering the patients

Table 1
Demographics (A), and age and sex differences of patients and controls (B).

A				B				
patients	mean	N	SD	gender		mean age	N	SD
age (years)	50.4	92	12.4	female	HC	47.33	21	11.78
sex (% female)	46	42			PAT	48.11	42	12.76
number of ECTs	12	92	4.1		Total	47.85	63	12.35
electrode position (RUL/BIL/LART/switched)	69/12/3/8			male	HC	51.63	22	11.58
initial HAMD	26.1	92	7.0		PAT	52.32	50	11.90
final HAMD	11.4	92	7.4		Total	52.11	72	11.73
initial MMSE	27.9	39	1.9	Total	HC	49.53	43	11.74
final MMSE	27.9	37	3.5		PAT	50.40	92	12.41
response rate (%)	62%	57			Total	50.12	135	12.16

HC: healthy controls, PAT: patients, RUL: right unilateral, BIL: bilateral, LART: left anterior right temporal, SD: standard deviation, HAMD: Hamilton depression scale, MMSE: Mini mental State Examination.

with the highest HAMD scores (31.8) and Marburg the lowest HAMD scores (19.2). The post ECT scores of the HAMD were not significantly different between sites ($F = 2.3$; $df = 5$; $p = 0.055$), whereas the percentage of decrease was significantly different ($F = 6.5$; $df = 5$; $p < 0.001$).

Overall 47% of the patients remitted and 62% responded to the treatment. Sites revealed different response rates (%response/ n = number of patients): Aachen 50% (n = 20), Heidelberg 91% (n = 12), Mannheim 78% (n = 18), Münster 57% (n = 28), Marburg 33% (n = 9), Göttingen 80% (n = 5).

A mean number of 12 ± 4.1 individual ECT sessions was administered, with differences between sites ($F = 2.4$, $df = 5$, $p = 0.039$, varying from 10 to 14).

Whole-brain volume changes

We found a mean increase of 2.2% in the relative whole brain gray matter (GM) volume in MDE patients after ECT. This increase, which was also indicated by a 2×2 ANCOVA ($f = -6.6$, $df = 1$, $p = 0.011$), was observed on an individual level in the majority of the patients but relative gray matter in HCs did not change. Both groups did not show any significant change in relative white matter volume (WMV).

Regional volume changes: whole-brain analysis

The GM adjusted and normalized images of the Jacobian rate represent the voxel wise volume changes over time. A one-sample *t*-test was conducted to test for significant local changes (mean value greater than zero representing an increase in volume, mean value lower than zero represents a decrease in volume).

There was no volume decrease in any region for the whole sample. In the right hemisphere a huge cluster of gray matter showed an increased volume after ECT (see Fig. 1 and Table 2).

The maximum change (maximum significant voxel) was located in the right parahippocampal gyrus. At a significance level of 0.05 (FWE corrected) only two additional other local maxima occurred – one in the amygdala and one in the superior temporal gyrus. This cluster however covers most of the temporal lobe as well as the hippocampus and the amygdala. A second cluster was located in the occipital lobe. The volume increases in the left hemisphere covered the amygdala and the hippocampal area.

An analogous one-sample *t*-test in the healthy control group did not reveal any volume increases or decreases. The two-sample *t*-test, comparing the Jacobian rates of patients and healthy controls revealed that volume increases were also significantly greater in patients.

Regional volume changes: ROI analysis

Hippocampus ROI analysis. A ROI analysis of the hippocampal area of patients showed that the whole length of the hippocampus was affected (Fig. 2, one-sample *t*-test, $p < 0.05$ FWE small volume corrected).

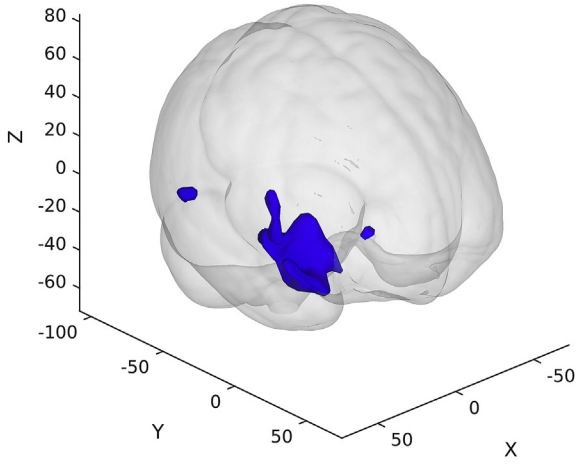

Fig. 1. Gray matter volume (GMV) increase after ECT: whole brain analysis ($p = 0.05$ FWE corrected on voxel level).

Extracted GM values (eigenvalues of hippocampus) verified that the volume increase within the hippocampus was not caused by WM decrease or a difference in the signal intensity. GM values increased significantly, whereas WM values did not change (see Table 3).

Amygdala ROI analysis. GM amygdala volume also increased as shown by the ROI analysis (one-sample *t*-test, $p < 0.001$ FWE small volume corrected, see Fig. 1, and Table 2 (bottom)).

Habenula ROI analysis. The region of interest analysis revealed no significant change within the mask, located around the habenula coordinates [48].

Cross-sectional analysis

Whole brain analysis showed no difference between GM volume of healthy controls and patients neither pre nor post ECT.

Clinical correlations

None of the clinical variables and their changes showed a significant influence on GM volume changes. Nor were the clinical variables correlated with the initial GM volume.

Post hoc we specifically analyzed 69 from the 92 patients, who received right unilateral ECT. This subgroup did not significantly differ regarding GMV increases. These increases again showed no correlations with any of the above mentioned clinical parameters

Table 2
Gray matter volume (GMV) changes, whole brain VBM analysis.

		x	y	z	cluster size (voxel)	P (FWE-corrected)	T	Z
Whole brain analysis								
Parahippocampal gyrus/hippocampus	**right**	**14**	**−2**	**−21**	**4387**	**0.000**	**7.38**	**6.50**
Temporal pole/insula	***right***	*34*	*10*	*−24*		*0.000*	*5.90*	*5.40*
Insula/hippocamus	***right***	*39*	*−14*	*−14*		*0.002*	*5.52*	*5.11*
Insula/temporal pole	**right**	**44**	**−2**	**−3**	**367**	**0.004**	**5.28**	**4.91**
Midddle temporal gyrus	**right**	**46**	**−62**	**−3**	**48**	**0.011**	**5.00**	**4.68**
Parahippocampal gyrus/hippocampus/Amygdala	**left**	**−14**	**−2**	**−21**	**66**	**0.014**	**4.93**	**4.62**
Region of interest analysis								
Hippocampus	right	18	−4	−16	1663	0.000	6.99	6.22
Hippocampus	left	−14	−4	−21	1098	0.000	4.73	4.45
Amygdala	right	20	−4	−16	570	0.000	6.92	6.12
Amygdala	Left	−18	−2	−21	488	0.000	4.57	4.32
Habenula	Right					n.s.		
Habenula	Left					n.s.		

Bold rows: cluster maxima, italic: other local maxima within the same cluster, minimal distance 8 mm; * small volume FWE corrected. Whole brain analysis: peak voxel and maximal 3 adjacent local maxima, minimal cluster size 100, $p < 0.05$ FWE whole brain corrected, ROI analysis: peak voxel, $p < 0.05$ small volume FWE corrected, age and sex as covariates.

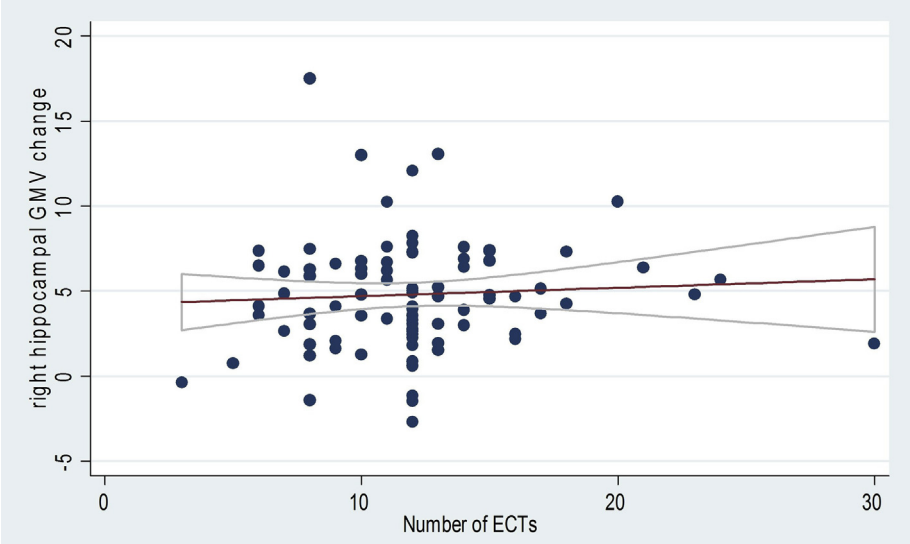

Fig. 2. Right hippocampal (GM) volume change versus number of ECTs applied.

or their changes. Non-responders showed a numerically, but not significantly greater GMV increase.

Only within the local analysis habenula volume changed over time (see Table 3). The change of mean value within the habenula mask significantly covaried with the number of ECTs applied (see Supplementary Table 5).

Discussion

The main finding of this large, pooled multicenter study is a highly significant gray matter volume increase of 2.2% after a course of ECT. This growth is not equally distributed over the cerebral cortex, but highly focused on temporo-mesial regions covering parahippocampal gyrus, insula, superior temporal gyrus, middle occipital & inferior temporal gyrus, inferior occipital & inferior temporal gyrus (see Fig. 1). Growth is not due to white matter volume loss and is lateralized towards the right hemisphere.

The total GM increase is of comparable size (2.2% versus 3.7%) to a subsample of 18 patients recently published [32]. No other total GM increase quantification following ECT was available from the literature. Overall lateralization of GM growth was mostly reflected within the hippocampal formation and thus discussed below.

Based on the existing literature on GM increase within the hippocampus and the amygdala, we performed a ROI analysis, which revealed a significant GMV increase within both structures, again significantly pronounced on the right side. Two of the previous studies showed a larger rise on the left side [25,39], the latest meta-analysis revealed no overall difference, but still a numerical difference with larger right-sided hippocampi [26]. Another recent pooled multicenter study corroborates a numerically higher volume increase of the right hippocampus [49]. Contrasting our results electrode position had an influence on left hippocampal GM growth (BL > RUL) [49]. On the other hand the idea that electrode position does not influence laterality of GM increase might be corroborated by the findings (a left-sided lateralization) of Nordanskog et al. and Redlich et al. since their patients had not received left-sided unilateral ECT [25,39]. No clear dependency from electrode position might fit to early animal findings, which failed to report large field gradients inside the brain (most of the gradient was found at scalp, bone and cortical surfaces) [50]. How this lateralization to the right can be explained, remains unclear, but it could be associated by the underlying disease itself, since functional brain abnormalities in the right hemisphere have been frequently reported in mood and stress related disorders. Findings

Table 3
A: mean values of the regions of interest, extracted from the gray and white matter within the hippocampus, amygdala and habenula mask; time*group interaction – result of a linear mixed model, site and gender as co-factors, age as covariate.

modulated voxel value			MDD Patients				Healthy controls			Time *group inter-action		
			mean (std) pre ECT	mean (std) post ECT	SMD	Cohen's d	mean (std) pre	mean (std) post	SMD	F value	df	p
Hippo-campus	left	GM	.451 (.056)	.466 (.055)	.194	0.270	.451 (.035)	.453 (.034)	0.030	32.2	1/133	0.000
	left	WM	.207 (.068)	.209 (.072)	.012	0.029	.195 (.018)	.193 (.019)	-.079	9.2	1/133	0.003
	right	GM	.411 (.072)	.430 (.075)	.178	0.258	.422 (.030)	.423 (.030)	.013	67.3	1/133	0.000
	right	WM	.221 (.032)	.221 (.031)	.007	0.000	.223 (.021)	.222 (.020)	-.046	2.9	1/133	0.089
amygdala	left	GM	.599 (.073)	.621 (.074)	.206	0.299	.591 (.046)	.596 (.045)	.076	23.1	1/133	0.000
	left	WM	.125 (.121)	.127 (.127)	.013	0.016	.100 (.012)	.099 (.013)	-.072	7.8	1/133	0.006
	right	GM	.534 (.120)	.563 (.128)	.165	0.234	.552 (.043)	.553 (.045)	.009	69.7	1/133	0.000
	right	WM	.142 (.024)	.143 (.023)	.018	0.043	.148 (.020)	.147 (.018)	-.043	1.7	1/133	0.196
habenula	left	GM	.591 (.110)	.612 (.117)	.130	0.185	.586 (.071)	.595 (.069)	.085	3.7	1/133	0.055
	left	WM	.097 (.077)	.098 (.082)	.001	0.013	.083 (.012)	.082 (.013)	-.069	0.7	1/133	0.401
	right	GM	.327 (.083)	.337 (.088)	.084	0.117	.338 (.036)	.339 (.035)	.021	6.2	1/133	0.014
	right	WM	.049 (.012)	.049 (.012)	-.039	0.000	.050 (.008)	.050 (.009)	-.045	0.1	1/133	0.794

B: estimated gray matter volume of amygdala, hippocampus & thalamus, time*group interaction – result of a linear mixed model analysis, site and gender as co-factors, age as covariate

Estimated volume			Patients					Healthy Controls				Time *group inter-action		
			pre ECT	post ECT	% volume change	SDM	Cohen's d	t1	t2	% volume change	SDM	F value	df	p
Relative GM Volume	Whole brain		.442 (.041)	.452 (.039)	2.239 (3.998)	.164	0.232	.449 (.046)	.449 (.043)	0.270 (3.833)	.010	8.2	1/133	0.005
Hippo-campus	left	GM V	3.345 (.412)	3.458 (.407)	3.508 (3.57)	.194	0.276	3.347 (.256)	3.358 (.254)	0.347 (2.22)	.030	32.0	1/133	0.000
	right	GM V	3.160 (.388)	3.307 (.389)	4.806 (3.31)	.269	0.378	3.134 (.220)	3.139 (.222)	0.171 (2.15)	.016	84.6	1/133	0.000
amygdala	left	GM V	1.044 (.127)	1.080 (.129)	3.593 (3.66)	.201	0.281	1.029 (.081)	1.038 (.078)	0.962 (2.59)	.083	19.9	1/133	0.000
	right	GM V	1.102 (.125)	1.162 (.127)	5.524 (3.54)	.335	0.476	1.083 (.083)	1.084 (.088)	0.123 (2.78)	.012	83.7	1/133	0.000
thalamus	left	GM V	2.400 (.375)	2.473 (.400)	3.182 (6.16)	.135	0.188	2.413 (.248)	2.441 (.239)	1.258 (4.04)	.080	4.2	1/133	0.044
	right	GM V	2.490 (.355)	2.561 (.379)	2.972 (6.65)	.137	0.193	2.469 (.197)	2.474 (.186)	0.330 (3.79)	.020	6.7	1/133	0.011

Standard mean difference SMD=(mean_postECT-mean_preECT)/sqrt(variance_preECT+vaiance_postECT).
time*group interaction after excluding the variance explained by other predictors (age, gender, site).
Cohen's d – {(postECT_mean - preECT_mean)/standard deviation}; values greater than 0.2 indicate a medium effect.

of a recent meta-analysis of first episode depression revealed a slightly smaller right hippocampus (−4.0% left and −4.5% right) [51], which might corroborate such a view, as well as a recent report on a right sided reduction of pro-BDNF in a post mortem study [52]. Additionally, from a functional perspective the Danish/PET depression project has shown a greater regional cerebral blood flow within the right hippocampus compared with controls and compared with the left one in patients, who had been treated longer than one week [53].

With our large sample, we specifically wanted to address the question if basic clinical features like age, sex, initial severeness of the illness, improvement of depressive symptoms and change of cognitive measures correlate with local or global GM changes due to ECT. It might seem counterintuitively, but as hypothesized we did not find such correlations or covariations at all. This supports the findings of many other studies conducted before, especially with respect to a recent meta-analysis on hippocampal changes [26]. Nevertheless, Dukart et al. (n = 10) [28], Joshi et al. (n = 29) [27] and Cano et al. (n = 12) [54] were able to detect a correlation of symptom improvement with right hippocampal complex growth, growth of both hippocampi (and amygdala) and left medio-temporal lobe growth, respectively. Additionally, Bouckaert et al. detected a correlation between the percentage volume increase in the caudate nucleus region and an assessment score of psychomotor changes [55,56], while also failing to detect a coevolution of gray matter growth and amelioration of depression in a large sample of late-life depression patients [57]. Redlich et al. described a pronounced correlation of subgenual cingulate GM volume increase and HAMD change [39]. All these findings would still allow a hypothesis that a GM increase reflects a necessary, but not a sufficient (pre-) condition for a clinical ECT response. Again, such an unspecific (while still regionally focused) GM growth might also explain ECT's unspecific effectiveness on a variety of clinical syndromes like depression, psychosis, catatonia, mania, delirium, parkinsonism, suicidality, autoaggression and agitation. The missing observation of an association of serum BDNF increase post ECT and clinical outcome – as identified by a recent meta-analysis [58] further corroborates our findings within the neurotrophic hypothesis. Further evidence comes from a recent study comparing ECT induced GM increase between two diagnoses, i.e. major depressive episode and schizophrenia, failing to identify any disease-related differences [40]. Additionally, the only study investigating the long-term GM increase after ECT observed a return to baseline after six months [29], which also might be supportive of the hypothesized necessity of such a GM rise due to the clinical knowledge that within the same time frame most patients relapse if not receiving highly efficacious relapse preventing treatments [59].

Following the neurotrophic hypothesis of depression a positive association between GM increase and number of ECTs applied could be expected. Oltedal et al. [54] described such a relationship for hippocampal GMV changes. In our sample this relationship (i.e. right hippocampal volume increase versus number of ECTs, see Fig. 2 and Supplementary Table 3b) failed to reach the significance level (p = 0.10), which could be explained by a weak relationship (and a power problem of our sample).

We did not find any additional differences when including healthy controls into our analyses. Specifically, we did not detect differences between healthy controls and depressed patients before receiving ECT. This contrasts many earlier studies, especially studies investigating completely untreated (drug-naïve) depressed patients [60]. In such studies hippocampal and temporo-mesial GM loss was detected, sometimes even correlating with severeness of the current episodes or the cumulative duration of all previous episodes [61]. It has been shown that pharmacotherapy provides a protective effect regarding GM loss due to depressive episodes [8]. Therefore, it is a limitation of our study that we have no clinical information about amount and duration of concurrent psychotropic medication, but it is definite that most if not all patients received some kind of antidepressant drug regime before and/or during ECT due to clinical practice [62]. In that sense our results might be interpreted as a superior efficacy of ECT compared to antidepressants to induce a cortical GM increase. This view is supported by preclinical findings showing a greater brain-derived nerve growth factor (BDNF) increase in the central nervous system (CNS) with ECT as compared with antidepressants [13,63]. While, speculatively, changes of nerve growth factors with ECT [13] induce changes of neuroplasticity, it seems clear that not neurogenesis alone is responsible for GM volume changes [64,65].

Summing up, our results are corroborative of the idea that ECT exerts neurorestorative effects on structures including the hippocampal formation, which were compromised due to a gray matter loss during depressive episodes [11,32,66,67]. In that context it is also important to emphasize that we did not find any evidence for longitudinal GM loss due to ECT anywhere within the brain. Therefore, our study enhances existing evidence falsifying older dogmas of ECT inducing “brain damage”.

Motivated by a post mortem study [31] and high-resolution magnetic resonance imaging studies [32,33] we conducted a post hoc analysis of habenula GM volume. While within the time × group interaction the GM voxel value of the habenula sphere reveals significant increases for both hemispheres (Table 3), no significant result was observed in the pre-post VBM analysis regarding a GM volume increase (Table 2). This discrepancy might reflect two major limitations of the “habenula” analysis. On the one hand the sphere is rather small and not manually or individually located and on the other hand the analyzed brain region is a typically artifact rich region.

Additional general limitations of our study can be derived by basically from its design: Due to the retrospective character it was not possible to gain further clinical information of the included patients (like e.g. concurrent drugs, degree of treatment resistance, length of the current episode or number of previous episodes, presence of psychotic symptoms, bipolar/unipolar depression, further comorbidities, immobilization, etc.). Of course, the MMSE is a crude measure of cognition and we cannot exclude from our data that a more differentiated psychometry would reveal e.g. a correlation of GM changes and ECT side effects. Different included centers showed different parameters regarding inclusion or dropout rates, ECT, and imaging, but results did not change when center number was included as a cofactor or when single centers were excluded from analysis. Additionally, a second control group of depressed inpatients not treated with ECT should be included in future studies.

Conclusions

To the best of our knowledge our study reports the largest cohort of depressed patients corroborating hippocampal and amygdala growth due to ECT. Specifically, temporal GM volume increase with a pronunciation to the right hemisphere was significant on a whole brain level. We identified no clinical parameter (i.e. initial HAMD, initial MMSE, HAMD change, MMSE change, response, remission, age, sex, number of ECT sessions) covarying with GM growth. This might be supportive for a rather unspecific effect of ECT on GM growth.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.11.017.

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