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ARTICLE

Volume increase in the dentate gyrus after electroconvulsive therapy in depressed patients as measured with 7T

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Abstract

Electroconvulsive therapy (ECT) is the most effective treatment for depression, yet its working mechanism remains unclear. In the animal analog of ECT, neurogenesis in the dentate gyrus (DG) of the hippocampus is observed. In humans, volume increase of the hippocampus has been reported, but accurately measuring the volume of subfields is limited with common MRI protocols. If the volume increase of the hippocampus in humans is attributable to neurogenesis, it is expected to be exclusively present in the DG, whereas other processes (angiogenesis, synaptogenesis) also affect other subfields. Therefore, we acquired an optimized MRI scan at 7-tesla field strength allowing sensitive investigation of hippocampal subfields. A further increase in sensitivity of the within-subjects measurements is gained by automatic placement of the field of view. Patients receive two MRI scans: at baseline and after ten bilateral ECT sessions (corresponding to a 5-week interval). Matched controls are also scanned twice, with a similar 5-week interval. A total of 31 participants (23 patients, 8 controls) completed the study. A large and significant increase in DG volume was observed after ECT ($M = 75.44$ mm^3, std error = 9.65, $p < 0.001$), while other hippocampal subfields were unaffected. We note that possible type II errors may be present due to the small sample size. In controls no changes in volume were found. Furthermore, an increase in DG volume was related to a decrease in depression scores, and baseline DG volume predicted clinical response. These findings suggest that the volume change of the DG is related to the antidepressant properties of ECT, and may reflect neurogenesis.

Introduction

Electroconvulsive therapy (ECT) is the most potent psychiatric treatment [1–5], with effect sizes of 1–1.5 for severe and refractory unipolar and bipolar depression [1–4, 6]. ECT convincingly outperforms pharmacotherapy such as tricyclic antidepressants and monoamine oxidase inhibitors, and any form of psychotherapy [1, 2, 4].

Despite its outstanding performance in reducing depressive symptoms up to the point of full remission, the working mechanism of ECT remains partly unknown. In preclinical studies, electroconvulsive seizure (ECS; the animal analog of ECT) has been used to study the underlying neurochemical and neurobiological effects of ECT, with the hippocampus as the main focus [7–10]. Both in rodents and in non-human primates, neurogenesis in the dentate gyrus (DG; but not in any of the other hippocampal subfields) following ECS has been reported as a robust effect [8, 9, 11–14]. In addition to neurogenesis, angiogenesis, gliogenesis, mossy fiber sprouting, dendritic arborization, and synaptogenesis have also been observed as a result of ECS

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[11, 15–18]. These processes can be observed in several regions of the adult mammalian brain, within and outside the hippocampus [19–22].

Several neuroimaging studies in patients undergoing ECT for unipolar or bipolar depression have investigated hippocampal volume [23–32]. Recent meta-analytic and literature reviews summarizing these studies report significant increases in volume of both the left and right hippocampus and both amygdala [33–35]. Recently, the Global ECT-MRI Research Collaboration (GEMRIC [36]), including a large sample of depressed patients, replicated these results [32]. While this finding supports a possible role for neurogenesis in the clinical effects of ECT, other functional recovery processes of the hippocampus, such as angiogenesis or gliogenesis could also account for the increase in hippocampal volume. It therefore remains unclear if ECT in (human) depression elicits the same effect as in animal models, and especially if neurogenesis in the DG plays the same crucial role. A recent study in healthy humans showed that neurogenesis was not present in the adult brain [37]. This finding has been debated [38] and as for now, it remains undecided whether or not the adult human brain is at all capable of neurogenesis.

Accurate volumetric information from subfields of the hippocampus could help to differentiate between effects caused by neurogenesis (restricted to the DG) and effects of other processes, such as angiogenesis and synaptogenesis (affecting all hippocampal subfields). Therefore, accurately delineating the hippocampal subfields is of utmost importance to identify specific ECT-induced volumetric changes and decipher whether or not neurogenesis takes place in humans during ECT. This is an important missing link, as neurogenesis may be a crucial mediating factor of the antidepressive effects. However, the hippocampus is a small structure and a very high-resolution scan is needed in order to accurately delineate its different subfields [39–41]. So far, effects of ECT have been studied on MRI scanners operating at 1.5- or 3-tesla magnetic field strength, restricting the maximum image resolution that can be achieved and therefore the level of precision for the segmentation of the hippocampal subfields [34, 39, 41–43]. A possibility to increase image resolution is to scan at ultra-high magnetic field strength (e.g., 7 tesla). For repeated measurements a further increase in sensitivity can be achieved by ensuring that the positioning of the scan with respect to the brain is kept constant for each scan session. In the current study, we therefore used a 7-tesla scan sequence that was designed for optimal measurement of the hippocampal subfields and employed fully automatic scan planning to ensure that the positioning of the scan within each subject was performed in the same way before and after ECT treatment.

We hypothesize that volume changes will pertain specifically to the DG as this structure has consistently been linked to neurogenesis in animal models of ECT. In addition, we hypothesize that the change in volume of the DG is positively related to the clinical effect (i.e., a greater increase in volume of the DG is associated with the beneficial therapeutic effects of ECT).

Materials and methods

Sample

Patients and controls were recruited at the Department of Psychiatry in the University Medical Centre (UMC) Utrecht, the Netherlands. For patients the following inclusion criteria were used: (1) age over 18 years, (2) a diagnosis of unipolar or bipolar depression (as defined by the DSM-IV-TR criteria [44]), and (3) an indication for ECT treatment (according to the Dutch Guidelines on Electroconvulsive Therapy [45]). Exclusion criteria for patients were treatment with ECT in 6 months prior to inclusion, contraindications for MRI (e.g., a pacemaker, claustrophobia, metallic implants), brain pathology, history of stroke, pregnancy and/or lactation, or any major medical condition (e.g., coronary heart disease, chronic obstructive pulmonary disease).

For healthy controls, an age over 18 years and absence of any psychiatric diagnosis constituted the inclusion criterion. In addition, we aimed to include controls with similar demographic characteristics (age, gender, years of education) as the patients. Exclusion criteria for controls were a (history of a) psychiatric illness (as assessed using the MINI interview, Dutch translation [46, 47]), contraindications for MRI, brain pathology, history of stroke, pregnancy and/or lactation, or any major medical condition. We note that the purpose of including healthy controls was to determine whether possible volume changes could be attributed to systematic variation in scanner characteristics (e.g., scanner drifts).

Written informed consent was obtained from all participants. This study was reviewed and approved by the local Medical Ethics Board at the UMC Utrecht. In total, 38 participants (26 patients, 12 healthy controls) met inclusion/exclusion criteria. Due to personal reasons (two patients and four controls), anxiety in the scanner (one patient, one control), less than ten ECT sessions (one patient), scanning artefacts (two patients, two controls at baseline, two patients at exit), a total of 30 participants (22 patients, 8 controls) were analyzed. This corresponds to 21 complete scan sets (16 patients and five controls) and a total of 51 scans that were included in the analysis (including the scans of

participants for which only a baseline or exit scan was available).

Treatment procedure

Using a Thymatron IV ECT machine (bifrontotemporal electrode positioning, with a stimulus intensity of 150% of the titrated seizure threshold), electroconvulsive therapy was given twice a week, for five consecutive weeks. After exactly ten sessions, patients were included in the exit assessment. This was to minimize variability of treatment duration between patients at exit. Afterward, when clinically indicated, some patients received additional ECT. One patient received less than ten ECT sessions and was excluded from the analysis.

Prior to delivering the electrical current, an anesthetic drug (etomidate/methohexital) and a muscle relaxant (succinylcholine) were administered. A blood pressure cuff was placed on the left or right arm to prevent the muscle relaxant from entering, allowing the length of the provoked seizure to be observed visually and by an electromyogram. Licensed anesthesiologists and nurses monitored the patients' vital signs during the entire session. A trained psychiatrist (or resident) administered the electrical current. Using a single channel (right frontomastoid placement) an electroencephalographical (EEG) recording was recorded. Following the Dutch Guidelines on Electroconvulsive Therapy [45] and international literature [48], a minimum motor seizure duration of 20 s had to be observed. If the motor seizure duration was <20 s, a new current was delivered with an energy increase of 5–10%. No more than three attempts per session were made. All patients had seizures of >20 s on each ECT session.

MRI data acquisition and processing

MRI data was acquired using a 7T magnetic resonance imaging (MRI) machine (Philips Healthcare, Best, the Netherlands) and a 32-channel head coil (Nova Medical, Wilmington, MA, USA). First, a 3D T1-weighted TFE scan was acquired (voxel size 1 mm isotropic; TR/TE 5.5/2.04 ms; flip angle 6°; FOV 256 × 256 × 190; number of slices 190; total scan duration 125 s). Next, a 3D T2-weighted TSE scan was acquired (voxel size 0.286 × 0.286 mm in plane resolution, 2 mm slice thickness; TR/TE 3800/60 ms; flip angle 90°; FOV 60 × 220 × 220; number of slices 30; total scan duration 494 s). Note that the voxels of this scan are highly anisotropic. For repeated measurements it is therefore crucial that the placement of the field of view (FOV) is planned for each measurement in the same way. To ensure this, we used so-called SmartExam planning. This is a fully automatic planning method to place the FOV on the brain based on a number of anatomical characteristics of the head extracted from a short T1-weighted scan acquired before each scan (see supplementary figure S1 for an example of two scans from the same subject scanned 5 weeks apart).

All processing was done with the Automated Segmentation of Hippocampal Subfields (ASHS) pipeline, FSL (5.0.9), and ANTs tools [49–52]. For a detailed outline of this pipeline, see Yushkevich et al. [49, 53, 54]. In short, the T2-weighted scan is aligned to the T1-weighted scan (rigid registration), then the T1-weighted scan is registered to the atlas template (implemented in ASHS) [49]. These registrations are applied to the T1- and T2-weighted scans to resample both scans into the template space of the regions of interest (ROIs; left and right). Then, the segmentations in the atlas package are registered to subject space. Afterward, multi-atlas joint label fusion [53] and voxel-wise corrective learning methods [54] are used to segment the hippocampus [49]. This automated procedure resulted in reduced observer bias. After the segmentation process, each segmentation was inspected visually and rerun or excluded if artefacts were present. Subfields included in the atlas were the DG, Cornu Ammonis 1–3 (CA1-3), entorhinal cortex (ERC), Subiculum (Subi), Collateral sulcus (CS), and Brodmann area 35 and 36 (B35, B36). Volumetric data for each subfield was subsequently exported and imported into R (version 3.4) and SPSS (IBM Corp., version 24).

Clinical effect (HAM-D)

To quantify the effect of ECT on depression within the patient group, the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) was administered at baseline and exit [55]. The HAM-D is widely used in clinical practice and scientific research to assess (changes in) depression severity [55, 56].

Statistical analyses

For each subfield separately, interaction effects between time (pre/post) and group (patients/controls) were tested with R (package lmerTest [57], R version 3.4.3 [58]) using a linear mixed model for repeated measures with time*group, age, and gender as fixed factors and hemisphere (left/right; modeled as slope for different subjects) and subject as random factors (modeled as intercept) [59, 60]. Linear mixed models with significant effects for time*group were further split up into two models for patients and controls separately, to test which group drives the effect. If the patient and/or control group showed significant effects for time in this latter analysis, a linear mixed model was conducted for the left and right DG separately to see which subfield drives the effect. To test whether the volume change of the DG significantly differed from the volume

change in the largest other subfield (i.e., the CA1 region), we conducted a paired *t*-test on the percentage increase for both the DG and CA1 region.

Additionally, we have run a repeated measures correlation analysis [61] to assess the relationship between Hamilton score and DG volume after regressing out the effects of age, gender, baseline hippocampal volume, and baseline depression scores. Also, we performed a linear regression with decrease in HAM-D (exit–baseline) scores as dependent variable and baseline volumes of the significant subfields in the linear mixed model as predictor and age (in years) and gender as covariates. Post hoc paired *t*-test were conducted as an additional analysis (see supplementary S2).

Effect sizes for change in volume for patients and controls separately are calculated as Cohen's d for paired observations for each subfield (left and right together). In addition, Cohen's d for paired observations is used to calculate the effect size of the mean change in Hamilton score.

Results

Sample

In total, 31 participants (23 patients, 8 controls) were included in the study (see Table 1). At baseline, the patients did not differ statistically from the controls in terms of age, gender, handedness, and IQ (Table 1). Due to dropout and scanning artefacts (see Materials and methods, section 'Sample') we obtained a total of 21 complete pairs (baseline/exit; 16 patients, 5 controls) and a total of 51 scans (26 baseline-scans, 25 exit scans). Hamilton score significantly decreased between baseline and exit ($t = 4.6$, $p < 0.001$, effect size = 0.958), see Table 1.

Table 1 Demographics of the sample

Variable		Patients	Controls	Diff	Statistic (test)	*p*
Total *N*		23	8	–	–	–
Age		50.3	49.25	1.054	0.165 (*t*)	0.87
Gender	Female	18	5	–	0.770 (χ^2)	0.38
	Male	5	3			
IQ		105.32	111.17	5.848	1.143 (*t*)	0.26
Handedness[a]	Left	2	1	–	Fisher's exact	1
	Right	21	6			

	Baseline (mean, SD)	Exit (mean, SD)	*t* (df)[b]	*p*	ES[c]
HAM-D	22.59 (7.39)	15.48 (8.15)	4.6 (22)	<0.001	0.958

χ^2 chi-square test statistic, *diff* difference, *N* number, *IQ* intelligence quotient, *p* *p*-value

[a] $n = 30$

[b] Paired *t*-test

[c] Effect size d for paired observations

Segmentations

In 51 scans the left and right hippocampus were automatically segmented. A segmentation is shown in Fig. 1 for the left hippocampus. The linear mixed model indicated a significant time*group effect for the DG ($t = -2.57$, $p = 0.0138$). None of the other subfields showed significant time*group effects (all $p > 0.05$, see supplementary S3). For patients, the DG showed a significant increase in volume from baseline to exit (mean change = 75.44 mm^3, 95% CI [56.5–94.3], std error = 9.65, $t = 7.82$, $p < 0.001$). For controls, the DG showed no increase or decrease in volume from baseline to exit (mean change = 22.69 mm^3, 95% CI [−7.0–52.3], std error = 15.13, $t = 1.5$, $p = 0.154$; see Table 2). Both left (mean change = 78.30 mm^3, 95% CI [54.3–102.3], std error = 12.25, $t = 6.39$, $p < 0.001$) and right DG (mean change = 70.14 mm^3, 95% CI [39.9–100.4], std error = 15.45, $t = 4.54$, $p < 0.001$) were significantly increased in the patient group from baseline to exit. See Fig. 2 for a visual representation of the estimated marginal means for the left and right DG in the patient group. See supplementary S6 for the output of the models referred to above. Paired samples *t*-tests indicated that the volume change in the DG was significantly greater than the volume change in the CA1 regions, for both the left DG (paired difference = 8.07%, $t(df) = 6.15(15)$, $p < 0.001$, 95% CI [5.28–10.87]) and the right DG (paired difference = 7.54%, $t(df) = 4.46$, $p < 0.001$, 95% CI [3.94–11.15]). A 3D rendering of the DG scanned at ultra-high field and its embedding in the hippocampus is shown in Fig. 1 (BA 35 and 36 are not shown). See supplementary materials (S5) for plots showing individual scores from baseline to exit for the DG. See supplementary S2 and S4 for results of the post hoc paired samples *t*-tests. Effect sizes for the mean change in DG volume are 1.49 (Table 2) for left and right together and 1.63 for the left DG and 1.22 for the right DG for patients (see supplementary S4 for all subfields for patients and controls).

Clinical variables

The repeated measures correlation analysis indicated a significant negative relationship (after regressing out the effects of age, gender, baseline Hamilton score and baseline DG volume) between Hamilton score and right DG ($r = -0.71$, $p = 0.001$, 95% CI [−0.90 to −0.31]) and the left DG ($r = -0.70$, $p = 0.002$, 95% CI [−0.89 to −0.28]). The negative relationship indicates that an increase in DG volume is associated to a decrease in Hamilton score. See

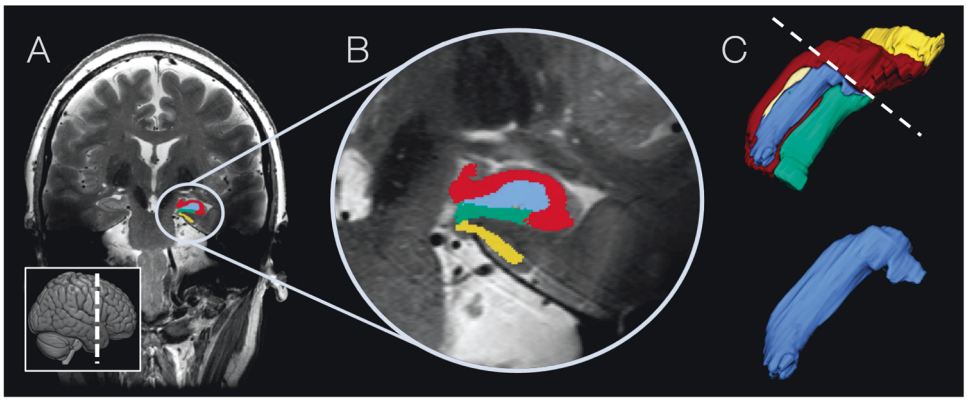

Fig. 1 Hippocampal subfield (left) segmentation and 3D rendering of the hippocampus and dentate gyrus. Panel (**a**) displays a whole brain T2-weighted scan showing the location of the hippocampus in a coronal slice. The location of the slice is presented in the left corner of the figure. Panel (**b**) displays the hippocampus subfield segmentation at the same position as panel (**a**) and is color coded: red = CA1; blue = DG; turquoise = subiculum, and desert = ERC. Panel (**c**) displays a 3D rendering of the hippocampus (upper) and the DG (lower). The dashed white line shows the positioning of the 3D hippocampus relative to panel (**b**). The same color coding as panel (**b**) is used for panel (**c**)

Table 2 Estimated marginal means for baseline vs. exit patients ($n = 22$) and controls ($n = 8$) (LMM)

	Group	Baseline[a]	Exit[a]	Diff	95% CI	*t*	df	Sig	ES[b]
DG	Patients	792.59	868.03	75.44	56.5–94.3	7.82	30.88	<0.001	1.489
	Controls	869.77	892.45	22.69	−7.0–52.3	1.5	15.27	.154	0.521

LMM linear mixed model, *Diff* difference between estimated marginal means for baseline and exit based on linear mixed model, *95% CI* confidence interval for difference between baseline and exit, *t* *t*-statistic, *df* estimated degrees of freedom (Satterthwait's method), Sig = *p*-value

[a]Estimated marginal means for left and right DG together (i.e., average)

[b]Effect size d for paired observations based on 16 available pairs

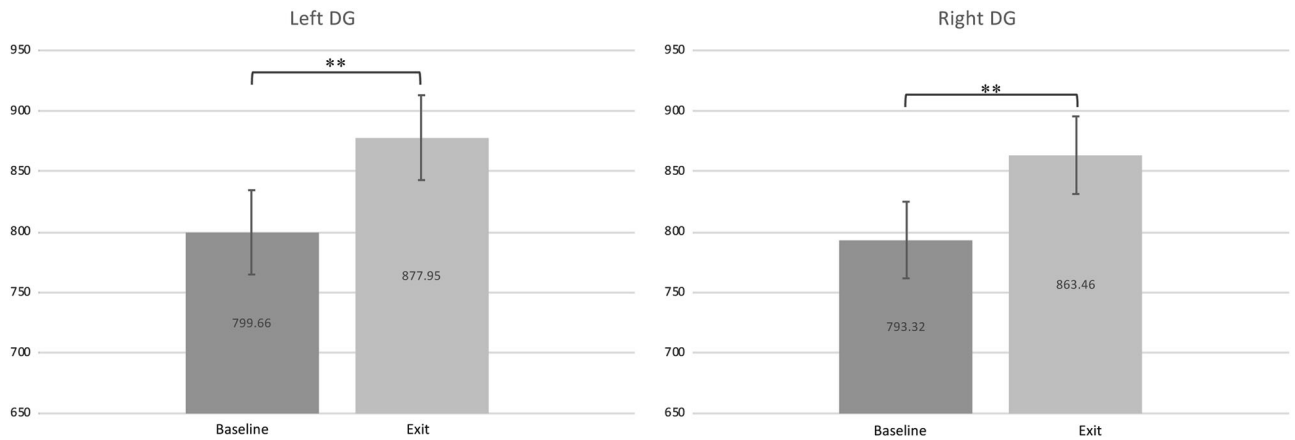

Fig. 2 Bar graphs of the estimated marginal means of the volume of the left and right DG for patients. Volume is displayed in mm^3; error bars represent standard error; ** = $p < 0.001$; estimated marginal means based on the linear mixed model for patients (left and right separately modeled)

Figs. 3 and 4 for a visual representation of this relationship with raw data points. See supplementary S7 and S8 for plots of the difference (baseline–exit) in Hamilton scores and DG volume change (exit–baseline).

The linear regression model predicting decrease in depression scores with baseline volumes of the left and right DG, gender and age was significant ($F(4,14) = 3.382$, $p = 0.039$) explaining 49.2% of the variance (see Table 3). Baseline hippocampal volume did not predict clinical effect ($p > 0.05$).

Discussion

We investigated the effect of electroconvulsive therapy on subfields of the hippocampus using ultra-high field MRI.

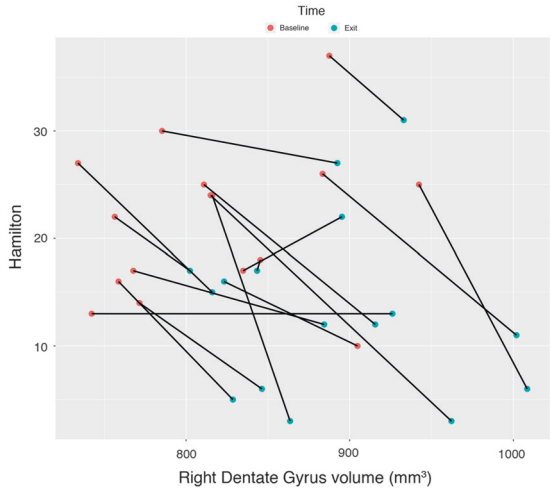

Fig. 3 Relationship between Hamilton and the right DG volume within subjects. Each line represents a single participant with each dot corresponding to two time points. The red dots represent the baseline measurement, the turquoise dots represent the exit measurement. A negative slope indicates that an increase in right DG volume is related to a decrease in Hamilton score. In other words, it displays the relationship between DG volume and Hamilton score within each individual. Volume (raw) is displayed in mm^3; Hamilton score is displayed as raw scores

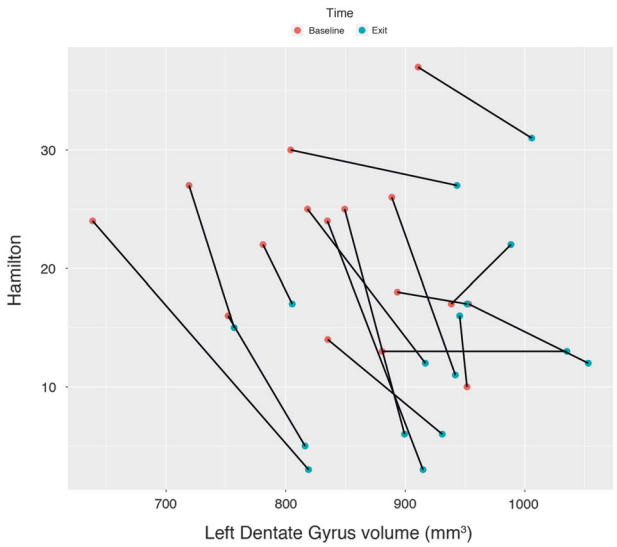

Fig. 4 Relationship between Hamilton and the left DG volume within subjects. Each line represents a single participant with each dot corresponding to two time points. The red dots represent the baseline measurement, the turquoise dots represent the exit measurement. A negative slope indicates that an increase in left DG volume is related to a decrease in Hamilton score. In other words, it displays the relationship between DG volume and Hamilton score within each individual. Volume (raw) is displayed in mm^3; Hamilton score is displayed as raw scores

Volume increases in the hippocampus during ECT were only found in the left and right DG, while other subfields were not affected. In addition, we showed that the increase in DG volume was related to the decrease in depression scores within individuals. These findings confirm our hypothesis that ECT increases the volume of the left and right DG in depression and point to neurogenesis as the mediating factor of anti-depressive effects. Indeed, baseline volume of the DG (together with age and gender) was a significant predictor of ECT effects, while total hippocampal volume at baseline was not. These findings suggest that the antidepressant effect of ECT is possibly mediated by neurogenesis and not by other physiological effects, such as angiogenesis, synaptogenesis, and sprouting, which would affect other hippocampal subfields as well.

Table 3 Linear regression predicting change in HAM-D score

Predictors	Beta	*t*	*p*
Left DG	−0.847	−3.43	0.004
Right DG	0.739	2.66	0.019
Gender	−0.346	−1.73	0.105
Age	0.103	0.496	0.628

Beta standardized coefficients, *t* statistic, *p* two-tailed *p*-value

Our results extend and complement clinical research into the effect of ECT on the hippocampus. Previous research has consistently shown volume increases in the left and right hippocampus [32–35]. We extend this finding by showing that these volume changes pertain to the DG. A possible reason why earlier neuroimaging studies found global increases [33–35] or in multiple subfields [26, 30], may be that these studies were performed on 3T MRI machines without employing automatic volume selection planning, potentially blurring findings on subfield volumes. Indeed, the ability of a 3T MRI machine to accurately measure and segment subfields of the hippocampus has been questioned [39, 41, 42].

Recent meta-analyses reported that ECT-induced increases in total hippocampus volume are not correlated with clinical improvement [32–35]. This finding is also observed in a recent study using a large sample [32]. We show, however, that volume changes in the DG are significantly associated with a decrease in depression scores (correcting for the effects of age and gender, baseline depression scores, and baseline hippocampal volume). Moreover, we show that baseline DG volume significantly predicted clinical effect, while baseline total hippocampal volume did not.

To date, the animal analog of ECT, ECS, has yielded substantial information regarding the possible underlying neurochemical mechanism of ECT in humans. Most notably, neurogenesis in the granular layer of the DG has been reported as a robust effect of ECS in rodents and non-human primates [8, 9, 11, 12, 14, 18]. However, the link between neurogenesis and the antidepressant effects of ECT remains unclear [14]. In the present study we could not

investigate the granular layer of the DG directly, however, our results corroborate these preclinical findings by showing a strong increase in volume, exclusively in the DG.

In addition to neurogenesis, ECS induces dendritic spine maturation of newly generated granular cells, and increases in dendritic spine density of mature granular cells [62]. Furthermore, ECS stimulates an increase of granular cell mossy fiber sprouting to the CA3 region [17, 63, 64]. ECS has been shown to give rise to synaptogenesis and dendritic branching in the CA1 region of the rat hippocampus [65, 66]. Another effect associated with ECS in rodents is angiogenesis and vascular remodeling in the DG and in the stratum lacunosum moleculare of the hippocampus [15, 67–69]. Interestingly, although angiogenesis and neurogenesis in the DG often coincide and have been proposed as being dependent [13, 70], research has shown that ECS can induce neurogenesis even in the absence of angiogenesis in the DG [67]. Last, ECS is able to induce gliogenesis in the molecular layer, granular layer, and hillus of the hippocampus [71, 72]. Our results are partly in line with these preclinical studies, confirming the possibility of neurogenesis in both the left and right DG, but not of other processes such as gliogenesis or synaptogenesis in other parts of the hippocampus. Nevertheless, the absence of volume increase in the CA regions cannot be taken as proof to exclude other processes, since subtle, non-significant increases may be missed in this small sample. In addition, the increase in volume in the DG could also comprise of different processes (including, but not limited to, neurogenesis). However, given the large volume increases of both DG and its association to clinical recovery, we interpret these findings as an indication of neurogenesis.

Interestingly, neurogenesis in the hippocampus in animals has also been linked to several memory functions [73]. In humans, neurogenesis in infancy underlies the effect of forgetting (e.g., in the process of infantile amnesia [74]). The integration of new neurons into the hippocampal circuitry, which changes and remodels this circuitry, might disrupt previously stored memories [74–77]. Interestingly, ECT has also been shown to induce transient cognitive impairment [78–80] and retrograde (autobiographical) amnesia [81]. Based on the observation that ECT induces neurogenesis in preclinical studies and induced a specific increase in volume of the DG in the present study, it could be hypothesized that the formation of new neurons and their subsequent integration in hippocampal circuitry might underlie memory-specific adverse side effects of ECT. If this hypothesis is true, then the anti-depressive effect of ECT should be coupled to memory deficits induced, which can be tested in larger cohorts, such as the GEMRIC database.

The observation that (1) adults with depression have smaller hippocampi [82, 83] and (2) antidepressants increase neurogenesis in the dentate gyrus of the hippocampus [84, 85] with a time gap corresponding to the delay between administration of antidepressants and clinical efficacy [85, 86], led to the formation of the neurogenic hypothesis of depression. While the link between neurogenesis and antidepressants has been clearly established [85–87], the question whether or not neurogenesis is responsible for the mechanism of action of antidepressant drugs remains under debate with some reports showing that antidepressants induce effects independent of neurogenesis, or neurogenesis independent of the antidepressant effect [14, 86–88]. In the current study we show that baseline DG volume could predict antidepressant efficacy, and that change in DG volume is associated to clinical efficacy. Since these findings are correlative in nature, future studies using high field MRI and larger cohorts should investigate whether neurogenesis resulting from ECT is causative or necessary for the antidepressant effect or if it is an epiphenomenon.

Our study has several limitations which limit the generalizability of the results. First of all, the sample size is relatively small (resulting in possible type II errors). In total, 51 observations were made, resulting in 21 baseline–exit pairs (16 patients, 5 controls). To obtain as much information as possible from the data we employed linear mixed modeling for repeated measures to test for the effect of ECT on hippocampal subfields. However, large scale MRI studies, such as coordinated and recently published by the Global ECT-MRI Research Collaboration (GEMRIC) remain warranted [32, 36]. Second, 65% of the patient sample received antidepressant medication at baseline and exit. Antidepressant treatment (e.g., pharmacotherapy with Selective Serotonin Reuptake Inhibitors but also other classes of drugs such as tricyclic antidepressants) is able to induce neurogenesis in rodents and non-human primates [84, 85, 89–91]. However, in our sample, antidepressants had been started many months (often years) before ECT and the dose of anti-depressive drugs was kept stable during ECT. Furthermore, patients who received antidepressant drugs at baseline did not differ in baseline DG volume from those who did not, neither did patients receiving antidepressant drugs at exit differ significantly in exit DG volume nor in the difference between baseline and exit volumes (all $p > 0.05$).

In conclusion, we report that ECT induces volume increases in the left and right hippocampus, observed exclusively in the DG. In addition, we show that the increase in DG volume is positively associated to clinical improvement, while volumes of other subfields were not associated with outcome. Finally, we report that baseline DG volumes (together with age and gender) significantly predict a decline in depression scores, yet baseline total hippocampal volume did not. This suggests that the DG,

and probably neurogenesis which takes place exclusively in the DG, play an important role in the antidepressant effect of ECT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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