

Articles

Shape and volume changes of the superior lateral ventricle after electroconvulsive therapy measured with ultra-high field MRI

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ABSTRACT

The subventricular zone (SVZ) of the lateral ventricles harbors neuronal stem cells in adult mammals. Rodent studies report neurogenic effects in the SVZ of electroconvulsive stimulation. We hypothesize that if this finding translates to depressed patients undergoing electroconvulsive therapy (ECT), this would be reflected in shape changes at the SVZ.

Using T1-weighted MR images acquired at ultra-high field strength (7T), the shape and volume of the ventricles were compared from pre to post ECT after 10 ECT sessions (in patients twice weekly) or 5 weeks apart (controls) using linear mixed models with age and gender as covariates.

Ventricle shape significantly changed and volume significantly decreased over time in patients for the left ventricle, but not in controls. The decrease in volume of the ventricles was associated to a decrease in depression scores, and an increase in the left dentate gyrus.

However, the shape changes of the ventricles were not restricted to the neurogenic niche in the lateral walls of the ventricles, providing no clear evidence for neurogenesis as sole explanation of volume changes in the ventricles after ECT.

1. Introduction

Depression is a highly prevalent psychiatric disorder (Kessler et al., 2005, 2003), posing substantial burden on patients' daily lives and their relatives (Saarni et al., 2007; Vos et al., 2012; Whiteford et al., 2013). While being a highly effective treatment for a depressive disorder, the exact working mechanism of electroconvulsive therapy (ECT) remains unknown (Pagnin et al., 2004; UK ECT Review Group, 2003). In recent years substantial progress has been made in uncovering the effects of ECT on the brain, indicating widespread volumetric changes on MRI after ECT (Gbyl and Videbech, 2018; Nuninga et al., 2019; Ousdal et al., 2020a). Yet, whether these changes are necessary or related to the antidepressant response of ECT remains subject of debate (Nuninga et al., 2020b, 2020c; Ousdal et al., 2020a, 2020b; Takamiya et al., 2019a). Also, the cellular mechanism underlying these volume changes remains unknown.

Substantial research into the mechanism of ECT has been directed towards the hippocampus. The hippocampus is a laminar structure and harbors the dentate gyrus (DG), a region where neurogenesis is thought to be possible throughout adulthood (Boldrini et al., 2018; Sahay and Hen, 2007; van Praag et al., 2002). The hippocampus, and in particular the process of neurogenesis within the DG, has been implicated in both the pathogenesis and the treatment of depression (Eisch and Petrik, 2012; Malberg and Schechter, 2005; Sahay and Hen, 2007). In preclinical studies, electroconvulsive stimulation (ECS), has been shown to induce strong neurogenesis in the dentate gyrus of rodents and nonhuman primates (Ito et al., 2010; Lamont et al., 2001; Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007), together with other neuroplastic effects [such as dendritic spine maturation, sprouting, synaptogenesis and angiogenesis (Vaidya et al., 1999; Wennström et al., 2003)] In patients, specific increases in volume in the dentate gyrus have been found, suggesting that neurogenesis (and other neuroplastic

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processes) may also take place in humans after ECT (Nuninga et al., 2019; Takamiya et al., 2019b). Interestingly, these volumetric changes were related to the antidepressant response of ECT (Nuninga et al., 2019; Takamiya et al., 2019a). The exact nature of these volumetric changes remains unknown, yet studies suggest that neurogenesis and more widespread neuroplastic changes contribute to this increase instead of vasogenic edema (Nuninga et al., 2020a; Yroni et al., 2019).

Given that ECT induces a generalized seizure and that it is associated with widespread changes in the brain, neuroplastic effects are not necessarily limited to the hippocampus. With respect to neurogenesis, the lateral walls of the ventricles (subventricular zone; SVZ) are also capable of generating new cells (Weickert et al., 2000; Weissleder et al., 2016), although it is unclear to what extent this is possible throughout adulthood in humans (Alvarez-Buylla and García-Verdugo, 2002; Hansen et al., 2010; Lim and Alvarez-Buylla, 2016; Quiñones-Hinojosa et al., 2006). To investigate whether ECT stimulates neurogenesis in the SVZ, we analyzed the shape of the ventricles in a group of patients with a depressive disorder undergoing ECT. A small control group was also scanned twice to test whether any changes found were due to scanner drift. In the present study, we explore changes in the volume and shape of the ventricles and hypothesize that if neurogenesis takes place in the SVZ, this would be reflected in a change in the shape of the lateral walls of the ventricle; the location of the SVZ.

2. Methods

2.1. Sample

Patients and controls were recruited at the University Medical Center Utrecht. Patients were included with the following inclusion criteria: 1) age over 18 years, 2) a diagnosis of a depressive disorder (as defined by the DM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*, 2000)), 3) an indication for ECT treatment [based on the Dutch guidelines on ECT (Broek et al., 2010)]. Exclusion criteria were: 1) treatment with ECT six months prior to the study, 2) contraindication for MRI (e.g. metallic implants), 3) history of stroke, 4) brain pathology, 5) pregnancy and/or lactation, 6) any major medical disease (e.g. coronary heart disease). Controls were included when they were over 18 years of age and had no (history) of a psychiatric disease [assessed by the MINI interview (Pangman et al., 2000)]. Controls were matched to the patient group based on demographic characteristics. All patients and controls provided written informed consent and the study was approved by the local ethics committee.

2.2. Treatment procedure

ECT was given twice a week with a Thymatron IV ECT machine (bifrontotemporal electrode positioning, delivering a current at 150% of the titrated seizure threshold). As the patients were included in this study were part of a study investigating hippocampal subfields, see Nuninga et al. (2019), for a detailed description of the ECT procedure. Patients were scanned before the first ECT sessions and after exactly 10 ECT sessions (i.e. after 5 weeks with a maximum of 48 h between the scan and the 10th ECT session) to minimize variability due to different

numbers of ECT sessions. Controls were scanned twice, with a similar 5-week interval yet without ECT.

2.3. Scanning procedure and data analysis

A T1-weighted 3D turbo field echo (TFE) multishot acquisition (voxel size 1 mm isotropic; TR/TE 5.5/2.1 ms; flip angle 6°; FOV 250 × 250 mm²; number of slices 190; total scan duration 149 s; TFE factor = 400, shot interval 3500 ms, inversion time = 1200 ms) was acquired using a 7 tesla (7T) MRI scanner (Philips Healthcare, Best, The Netherlands) and a 32-channel head coil (Nova Medical, Wilmington, MA, USA).

The T1-weighted scans were automatically segmented using FreeSurfer's automated pipeline for longitudinal studies, implemented in version 6.0 (Fischl and Dale, 2000; Fischl et al., 2004; Fischl et al., 1999; Reuter et al., 2010, 2012). The longitudinal pipeline of FreeSurfer creates an unbiased within subjects template, subsequently initializing processing for the individual timepoints using the information from the within subjects template (Reuter et al., 2012, 2010). This procedure results in increased sensitivity for subtle changes within subjects. All images and parcellations of the ventricles were inspected visually to detect and correct errors if needed. After segmentation, the volumes of the lateral ventricles were extracted and imported in R [version 3.4.3 (R Core Team, 2013)]. To investigate whether the volume of the ventricles changed from pre to post ECT we employed linear mixed modeling [package lmerTest within R (Kuznetsova et al., 2017)]. The first model (left and right ventricle were analyzed separately), contained time (pre/post ECT), group (patients/controls), the interaction term group*time, age and gender as fixed factors and subject as random factor (intercept). Afterwards, the models were split up to analyze patients and controls separately. This model included time (pre/post), gender, and age as fixed factors, and subjects as random factor (intercept). To see if possible volumetric increases would coincide with the antidepressant effect of ECT, we computed repeated measures correlation between ventricle volume and Hamilton scores (Bakdash and Marusich, 2017). Repeated measures correlation were also run to see if changes in ventricle volume were associated to changes in dentate gyrus volume [see (Nuninga et al., 2019) for the method for obtaining dentate gyrus volume, the patients included in the present study also participated in Nuninga et al., 2019]. In addition, the same analyses were run to see if ventricle volume was related to more widespread volumetric changes of the entire hippocampus.

Ventricle shapes were extracted from the FreeSurfer output and imported into SlicerSALT (version 3.0) for shape analysis. SlicerSALT [salt.slicer.org (Vicory et al., 2018)] is a project within the freely available software package slicer (www.slicer.org). To analyze the shape of the ventricle, spherical harmonic based point distribution models (PDM) were first computed and aligned to the standard brain (within FreeSurfer) using Procrustes alignment. After aligning all ventricles, the mean shape for both the pre and post measurements were computed.

The mean ventricle shape was also used to output the results of the statistical comparison between the pre and post-ECT shapes. Statistical comparison was done using Multivariate Functional Shape Data Analysis

Table 1
Demographics of the sample.

Variable	Patients	Controls	diff	Statistic(test)	p	
Total N	22	8	–	–	–	
Age	50.1	49.4	0.88636	0.149 (t)	0.88	
Gender	Female	16	5	–	0.008 (χ^2)	0.93
	Male	6	3			
IQ*	104.59	110.8	6.24	1.92 (t)	0.06	
	Baseline (mean, SD)	Exit (mean, SD)		t(df)†	p	ES‡
HAM-D	21(7.09)	15(7.4)		3.57 (15)	0.003	0.89

* $n = 26$ $\chi^2 =$ chi-square test statistic; diff = difference; N = number; IQ = intelligence quotient; p = p-value; † = paired t-test; ‡ = effect size d for paired observations.

Table 2
Volumetric data.

Region of interest	Group	Volume (SD) pre	Volume SD (post)
Ventricle left	patients	10,953.00 (5563.47)	10,456.46 (5224.67)
	controls	13,772.02 (7833.86)	16,312.62 (9932.31)
Ventricle right	patients	10,210.00 (5105.15)	9878.84 (4839.38)
	controls	14,050.11 (7511.54)	15,415.2 (7369.63)
Hippocampus left	Patients	5042.74 (725.47)	5293.041 (568.79)
	controls	5237.64 (579.30)	5667.22 (294.54)
Hippocampus right	patients	5083.75 (701.79)	5222.97 (736.76)
	controls	5436.55 (698.06)	5572.56 (379.00)
Dentate Gyrus left	patients	805.85 (140.95)	892.86 (129.02)
	controls	868.64 (103.56)	896.16 (34.69)
Dentate Gyrus right	patients	797.90 (113.79)	856.32 (125.32)
	controls	833.34 (101.91)	869.81 (30.32)

Volumetric data of each region of interest. The units are in mm³ with standard deviation between the brackets.

(MFDSA) (Vicory et al., 2018). We analyzed six models, the first two models (left and right ventricle separately) included time, group, group*time, age and gender as regressors. Then, the ventricles of the patients were analyzed with a separate model for left and right ventricle including, time, age and gender as regressors. To test whether shape changes associate to Hamilton scores, two additional models (for the left and right ventricles separately) were run including Hamilton scores. P-values lower than 0.05 were considered statistically significant. P-values were FDR corrected.

3. Results

3.1. Sample

In total, we included 22 patients and 8 controls for this study. Due to scanning artefacts, and dropout we were able to include complete pairs (i.e. a scan pre ECT and post ECT) of 16 patients and five controls. Patients and controls did not differ in baseline demographics (age, gender and IQ; see table 1). ECT significantly decreased depression scores ($p < 0.003$, Cohen's $d = 0.893$). Table 2

3.2. Ventricle volume

The first two linear models showed a significant time*group effect for the volume of the right ventricle ($t = 2.31$, $p = 0.033$), but not for the left ventricle ($t = 0.784$, $p = 0.443$). Both models showed significant effects for time for the volume of the ventricles (right, $t = -2.573$, $p = 0.0191$; left, $t = -2.66$, $p = 0.016$). When split up for patients/controls separately, the model indicated a significant effect of time on the volume of the right ventricle for patients ($t = -2.464$, $p = 0.0263$, effect size = 0.62), but not for controls ($t = 1.749$, $p = 0.178$, effect size = 0.88). For the volume of the left ventricle, a significant effect of time was found for patients ($t = -2.455$, $p = 0.027$, effect size = 0.61), but not for controls ($t = -0.929$, $p = 0.421$, 0.47). The repeated measures correlation indicated a significant and positive relationship between change in Hamilton score and volume for the left ($r = 0.522$, $p = 0.032$) and right ventricle ($r = 0.509$, $p = 0.037$), indicating that, within subjects, Hamilton scores decrease as ventricle volumes do (see supplementary S7 and S8 for scatterplots of Hamilton scores and ventricle volumes). Additionally, a significant within subjects negative correlation was found between volumetric changes in the left dentate gyrus and the left ventricle ($r = -0.595$, $p = 0.019$), but not in the right dentate gyrus and the right ventricle ($r = -0.49$, $p = 0.061$). The same results were found when correlating the volume changes of the whole hippocampus to changes in ventricle volume: the left ventricle and hippocampus were significantly correlated ($r = -0.517$, $p = 0.048$), whereas the right hippocampus and ventricle were not ($r = -0.01$, $p = 0.97$).

3.3. Shape analysis

The first two analyses showed a significant global interaction effect for the left and right ventricles. Fig. 1 shows areas on the ventricles that significantly changed in shape for this interaction effect. Supplementary figures S1 (left) and S2 (right) show the beta coefficients for the interaction effect of the linear model for the x, y and z axes plotted for the significant areas on the ventricles. When patients were analyzed separately, global significant changes in shape pre to post ECT were also found for the left and right ventricle. See Fig. 2 for the areas where the

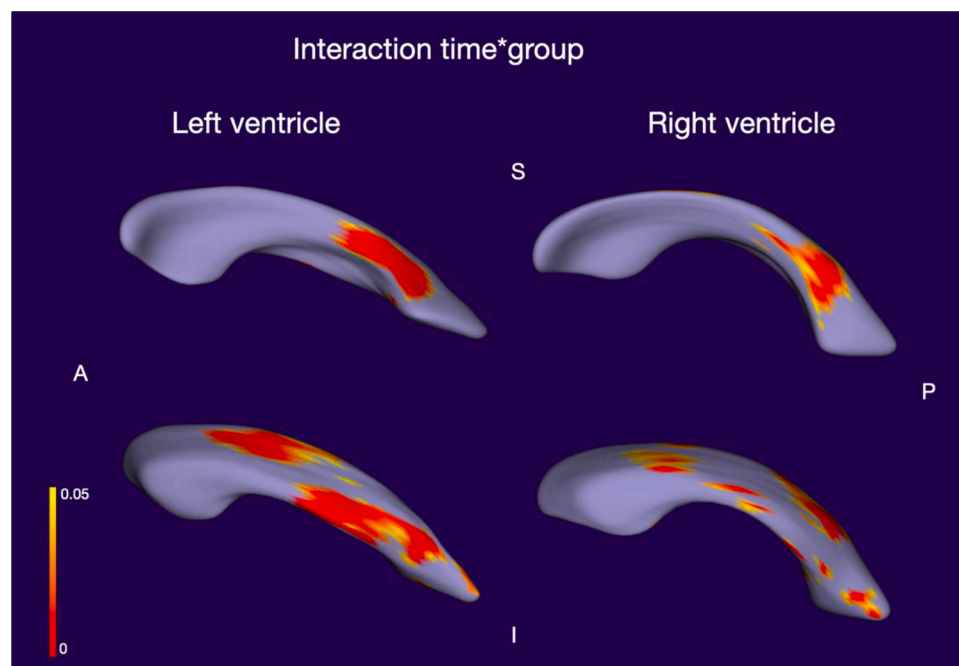


Fig. 1. On the left, two views of the left ventricle showing areas where the interaction effect between time and group (i.e. patients/controls) is significant. On the right, two views of the right ventricles showing areas where the interaction effect of time is significant. Color scale: yellow, $p = 0.05$, red, $p < 0.001$; A = anterior; P = posterior; S = superior; I = inferior.

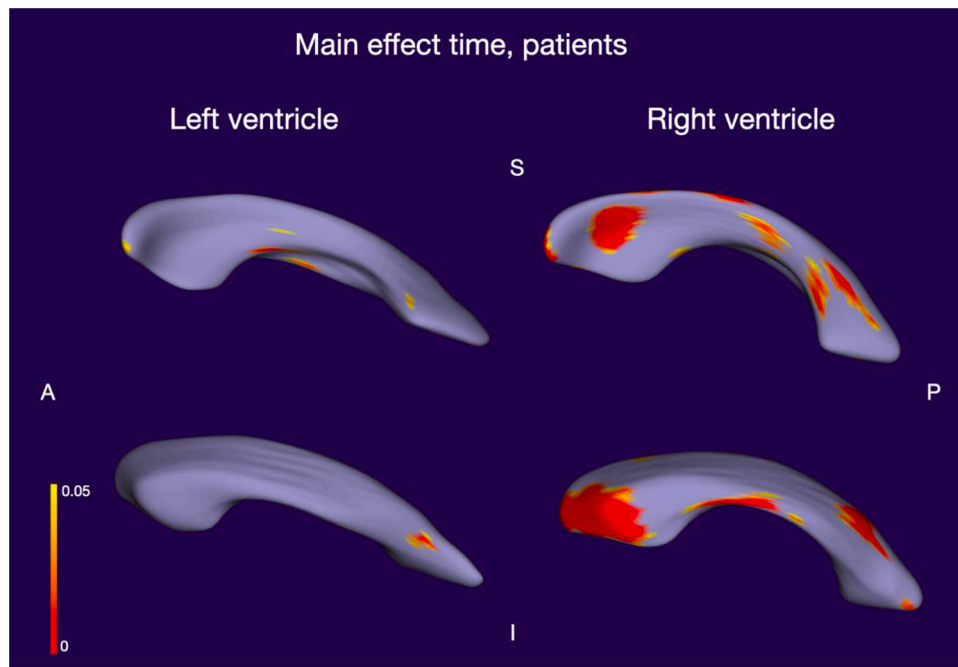


Fig. 2. On the left, two views of the left ventricle showing areas where the effect of time (for patients) is significant. On the right, two views of the right ventricles showing areas where the effect of time is significant. Color scale: yellow, $p = 0.05$, red. $p < 0.001$; A = anterior; P = posterior; S = superior; I = inferior.

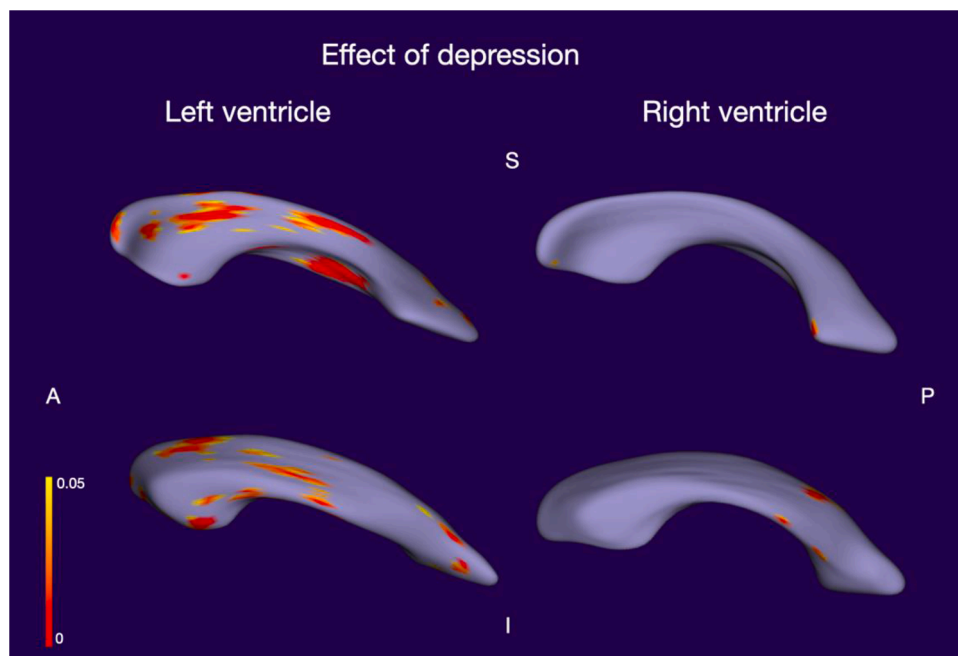


Fig. 3. On the left, two views of the left ventricle showing areas where the effect of depression (for patients) is significant. On the right, two views of the right ventricles showing areas where the effect of depression is significant. Color scale: yellow, $p = 0.05$, red. $p < 0.001$; A = anterior; P = posterior; S = superior; I = inferior.

ventricle significantly changed in shape over time in patients. Supplementary figures S3 (left) and S4 (right) show the beta coefficients of the linear model for the effect of time for three axes along x, y and z, again plotted for the significant areas. A global significant change along the ventricles was also found when looking at Hamilton scores, for the left and right ventricles. Fig. 3 shows the location of areas on the ventricles that were significantly associated with Hamilton scores. See supplementary figures S5 (left) and S6 (right) for the beta coefficients along x, y, and z for the significant areas along the ventricles.

4. Discussion

We investigated the effects of ECT on the volume and shape of the lateral ventricles. The main finding is that both the volume of the ventricle and its shape significantly change over time within individuals receiving ECT, but not in controls. The volume decrease in both right and left ventricle correlated with the decrease in severity of depression within subjects. The changes in shape did not pertain solely to the areas containing the subventricular zone (SVZ), making neurogenesis as the

sole explanation of volumetric changes in the ventricle unlikely.

These results are partly in line with emerging evidence showing that neuroplasticity, and especially neurogenesis explains (parts of) the effect of ECT. In animal research, it has been robustly shown that electroconvulsive seizures (ECS) stimulate neurogenesis (Ito et al., 2010; Madsen et al., 2000; Nakamura et al., 2013; Perera et al., 2007), and other neuroplastic processes such as synaptogenesis, angiogenesis and mossy fiber sprouting (Chen et al., 2009; Ekstrand et al., 2008; Gombos et al., 1999; Hellsten et al., 2005). To what extent these processes contribute to the antidepressant effects of ECT is an open question. Clinical studies directed at answering this question show widespread volumetric increases in the brain, and most consistently in the hippocampus (Gbyl and Videbeck, 2018; Ousdal et al., 2020a; Takamiya et al., 2018). More specifically, a strong increase in volume of the dentate gyrus (DG) of the hippocampus (the only region of this structure capable of neurogenesis) is observed, which could not be explained by edema (Nuninga et al., 2020a, 2019; Takamiya et al., 2019b). Interestingly, this increase in volume of the DG, but not in the other subfields, is associated with the decrease in depression severity within subjects (Nuninga et al., 2019; Takamiya et al., 2019a). Here, changes in volume of the left dentate gyrus were associated to changes in the left ventricles within subjects. The left ventricle was also correlated to the left hippocampus. For the right DG and the right ventricle, the analysis did not reach statistical significance. However, the difference of the strength of the correlation between DG and ventricle volume in the left hemisphere ($r = 0.595$) and the right hemisphere ($r = 0.49$) seems to be minimal (as are the p-values). Therefore, the absence of statistical significance should not be taken as evidence for pure laterality but might also be due to insufficient statistical power to pick up these effects.

Next to the DG, the subventricular zone of the lateral ventricles harbors neurogenic capacities in mammals (Conover and Todd, 2017; Quiñones-Hinojosa et al., 2006). In rodents, the neurogenic niches of the ventricles are well studied and defined, while in humans some questions remain unanswered (Akkermann et al., 2017; Conover and Todd, 2017; Quiñones-Hinojosa et al., 2006). Studies show that in normal human development, neurogenesis in the SVZ is ablated after two years of age (Coletti et al., 2018; Quiñones-Hinojosa et al., 2006). However, other studies report the existence (quiescent) neural stem cells up until later in adulthood (Donega et al., 2019; Quiñones-Hinojosa et al., 2006; Van Den Berge et al., 2010). Additionally, other neurogenic markers and neuroblasts have been found in both the lateral wall of the ventricles, and the adjacent striatal areas (Weickert et al., 2000; Weissleder et al., 2016). Considering ECT as a possible neurogenesis stimulating treatment, it is possible that ECT stimulates previously ablated neurogenesis in the SVZ. In rodent studies, seizure therapy increased neurogenesis in the SVZ both chemically (Parent et al., 2002) and electrically (Inta et al., 2013; Suzuki et al., 2007). Our results show that volumetric changes, and associated changes in shape, are not limited to the lateral wall of the ventricles. These findings do not strengthen the hypothesis that the effects of ECT on ventricle size are primarily due to neurogenesis in the SVZ, yet we cannot rule out that this process takes place and contributes to volume reduction and the antidepressant effect. A recent study showed that nearly all gray matter regions in the brain were increased in volume after ECT (Ousdal et al., 2020a), which provides an alternative explanation of the ventricle volume decrease and associated shape changes found in the current study. Future studies could set out to investigate this question.

The results of this study should be interpreted considering some limitations. The limited sample size is reducing the power to detect significant changes. Multi-site studies, such as coordinated by the Global ECT-MRI Consortium [GEMRIC (Oltedal et al., 2017)], are especially suited in overcoming this limitation. Increasing sample size is challenging at 7T MRI. While this is advantageous when imaging small structures demanding accurate delineation (such as the hippocampus), the ventricles are equally reliably imaged at 3T. Imaging at 3T is more feasible (both for the patients' tolerability, and cost effectiveness), and

thus could be used in future studies to maximize sample size. In addition, the time of the day of each scan might influence the results: it has been reported that brain volume decreases and ventricle volume increases during the day (Trefler et al., 2016). However, in our sample 7.8% of the 51 scans were not made during the morning (i.e. before 12 pm), yet before 3pm. Given this small percentage, we do not believe that this influenced the results reported here. However, in future studies, it is important to keep this in mind when scanning patients in a pre-post study.

In conclusion, in this study we report volumetric decreases of the lateral ventricles after ECT which correlate with the antidepressant effect. Ventricle size reductions were not reflected in site-specific alterations in shape. Our findings do not support the hypothesis that neurogenesis in the subventricular zone exclusively underlies the antidepressant effects of ECT. Future research could set out to investigate the causal mechanisms and the relevancy for the antidepressant effect of ventricle volume decrease.

Declaration of Competing Interest

None of the authors have conflicts of interest to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.psychres.2021.111384](https://doi.org/10.1016/j.psychres.2021.111384).

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