

## Original Article

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# Long-term effects of electroconvulsive therapy on brain structure in major depression

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**Abstract**

**Background.** Magnetic resonance imaging (MRI) studies on major depressive disorder (MDD) have predominantly found short-term electroconvulsive therapy (ECT)-related gray matter volume (GMV) increases, but research on the long-term stability of such changes is missing. Our aim was to investigate long-term GMV changes over a 2-year period after ECT administration and their associations with clinical outcome.

**Methods.** In this nonrandomized longitudinal study, patients with MDD undergoing ECT ( $n = 17$ ) are assessed three times by structural MRI: Before ECT ( $t_0$ ), after ECT ( $t_1$ ) and 2 years later ( $t_2$ ). A healthy ( $n = 21$ ) and MDD non-ECT ( $n = 33$ ) control group are also measured three times within an equivalent time interval. A 3(group)  $\times$  3(time) ANOVA on whole-brain level and correlation analyses with clinical outcome variables is performed.

**Results.** Analyses yield a significant group  $\times$  time interaction ( $p_{FWE} < 0.001$ ) resulting from significant volume increases from  $t_0$  to  $t_1$  and decreases from  $t_1$  to  $t_2$  in the ECT group, e.g., in limbic areas. There are no effects of time in both control groups. Volume increases from  $t_0$  to  $t_1$  correlate with immediate and delayed symptom increase, while volume decreases from  $t_1$  to  $t_2$  correlate with long-term depressive outcome (all  $p \leq 0.049$ ).

**Conclusions.** Volume increases induced by ECT appear to be a transient phenomenon as volume strongly decreased 2 years after ECT. Short-term volume increases are associated with less symptom improvement suggesting that the antidepressant effect of ECT is not due to volume changes. Larger volume decreases are associated with poorer long-term outcome highlighting the interplay between disease progression and structural changes.

**Introduction**

Major depressive disorder (MDD) is one of the most prevalent and disabling disorders worldwide (Murray *et al.*, 2012; Richards, 2011), of which therapy response presents a rather heterogeneous picture (Rush *et al.*, 2006). In patients with treatment-resistant MDD (Rush *et al.*, 2006), electroconvulsive therapy (ECT) has proven to be one of the most effective treatment options (The UK ECT Review Group, 2003). In particular, ECT – in accordance with the clinical practice guidelines for the treatment of depression (American Psychiatric Association, 2019) – appears to have a high efficacy in reducing psychotic symptoms and suicidality in MDD (Fink & Taylor, 2007). An emerging body of research has found ECT-related changes in brain structure (Enneking, Leeher, Dannlowski, & Redlich, 2019). Yet, conclusive research on the long-term stability of structural changes induced by ECT is largely missing.

Most studies focus short-term ECT-related structural changes. These studies revealed pronounced gray matter volume (GMV) increases, e.g., for the hippocampus-amygdala complex,

insula and anterior cingulate cortex (ACC) immediately after ECT (Enneking et al., 2019). GMV decreases were occasionally reported for prefrontal regions (Enneking et al., 2019). Regarding associations of structural changes with clinical response, neuroimaging studies present an inconsistent picture. The majority of studies in a previous review (Enneking et al., 2019) found no associations between short-term GMV changes and clinical improvement, suggesting that GMV changes after ECT are a by-product of ECT.

Due to the lack of long-term studies, it remains unknown whether these early ECT-induced GMV changes are persistent over time. Only a few neuroimaging studies have investigated GMV changes in MDD covering an interval of at least 6 months after ECT, with samples including 23 or less ECT patients at long-term follow-ups. The majority of these studies suggest that increases in volume and cortical thickness in the hippocampus, amygdala as well as frontal and insular cortex regions immediately after ECT are followed by decreases 6 months later (Bouckaert et al., 2016; Brancati et al., 2021; Gbysl et al., 2021, 2019; Nordanskog, Larsson, Larsson, & Johanson, 2014), with a return to pre-treatment levels (Bouckaert et al., 2016; Gbysl et al., 2021, 2019; Nordanskog et al., 2014). Another study by Jehna et al. (2020) with a follow-up time interval ranging from 10 to 36 months found no significant thalamic and hippocampal GMV decreases (Jehna et al., 2020). However, the results of this study might be confounded by the broad range of the reassessment interval (Jehna et al., 2020). In addition, only one of these longitudinal studies (Gbysl et al., 2021) found short-term GMV increases after ECT to be associated with immediate clinical improvement, while associations with delayed clinical improvement have not been studied so far.

There seems to be first evidence for the transience of short-term ECT-related structural changes. However, all of the mentioned longitudinal studies (Bouckaert et al., 2016; Brancati et al., 2021; Gbysl et al., 2021, 2019; Jehna et al., 2020; Nordanskog et al., 2014) are limited by the lack of a MDD non-ECT control group and occasionally by the lack of a healthy control group (Bouckaert et al., 2016; Gbysl et al., 2021, 2019; Nordanskog et al., 2014). This makes it difficult to disentangle the individual effects of ECT, time, medication and disease progression on these GMV changes. Additionally, while Bouckaert et al. (Bouckaert et al., 2016) only included participants with late-life depression, the other long-term studies (Brancati et al., 2021; Gbysl et al., 2021, 2019; Nordanskog et al., 2014), except of Jehna et al. (2020), also included participants with bipolar alongside unipolar depression. Yet, participants with late-life and bipolar depression are well known to differ from those with unipolar depression in terms of gray matter abnormalities (Khundakar & Thomas, 2009; Redlich et al., 2014).

Consequently, there is no sufficient research on the long-term stability of ECT-related GMV changes in MDD that compare to adequate control groups. Well-designed long-term studies would also shed light on long-term GMV changes after ECT and associations of GMV changes following ECT with delayed clinical outcome. Thus, the objectives were as follows: (a) to clarify the specificity of short-term GMV changes after ECT by involving a healthy and a MDD non-ECT control group and to replicate previous findings; (b) to investigate long-term GMV changes over the course of 2 years after ECT compared to both control groups; (c) to identify whether GMV changes immediately or 2 years after ECT are associated with clinical outcome.

## Materials and methods

### Participants and study design

All participants were part of the Münster Neuroimaging Cohort recruited from July 2010 to January 2018. The final study sample (For visualization of drop-out process, see online Supplementary Fig. S1) includes  $n = 50$  inpatients with acute MDD of which  $n = 17$  patients underwent ECT and  $n = 33$  received treatment as usual (TAU), meaning inpatient treatment with medication and psychotherapy. There is an overlap of nine patients within the ECT group and seven patients within the TAU group with a sample of a previous study (Redlich et al., 2016). Patients were recruited through the inpatient service of the Department of Psychiatry, University of Münster and of the Landschaftsverband Westfalen-Lippe hospital in Münster. Due to the naturalistic study design, the treatment protocol was based on clinical decisions independent from study participation. Additionally,  $n = 21$  healthy controls (HC) were recruited through public notices and newspaper announcements. Four participants in the HC group were also part of the previous study sample (Redlich et al., 2016). All participants were assessed at three time points: The ECT group completed structural magnetic resonance imaging (sMRI), the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck & Steer, 1987) before the start of ECT (Baseline/ $t_0$ ), immediately after completion of the ECT series (Post/ $t_1$ ) and approximately 2 years after baseline (Follow-up/ $t_2$ ). The TAU and HC group were also measured three times within an equivalent time interval following the same measurement procedure. To consider psychopharmacological treatment, a medication load index was computed for each time point according to the procedure described by Hassel et al. (2008). Each medication was coded as absent = 0, low = 1 (equal or lower than average dose), or high = 2 (greater than average dose) in relation to the midpoint of the daily dose range recommended by the Physician's-Desk-Reference (Reynolds, 2008). Then, for each participant and time point, a composite measure of total medication exposure was calculated by summing all individual medication. At  $t_0$  and  $t_2$ , diagnoses were verified employing the Structured Clinical Interview for DSM-IV (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) by trained clinical raters. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the ethics committee of the University of Münster (2007-307-f-S). Written informed consent was obtained from all participants.

Exclusion criteria for all participants were any neurological abnormalities or previous traumatic head injury, organic mental disorders, chronic medical diseases, benzodiazepine intake at study time or MRI contraindications. At  $t_0$ , all patients suffered from a current moderate to severe depressive episode according to DSM-IV (Wittchen et al., 1997) and were under inpatient psychiatric treatment. Further exclusion criteria for patients were a diagnosis of a bipolar disorder, a psychotic disorder or life-time substance dependence. Patients in the ECT group were defined as treatment-resistant according to Berlim and Turecki (Berlim & Turecki, 2007), as they failed to respond to at least two adequate antidepressant trials. They received adjuvant psychopharmacological medication during the ECT series. Patients in the TAU group never received ECT before  $t_0$  nor at any time between study time points. Further exclusion criterion for HC was any life-

time diagnosis of psychiatric disorder according to the SCID-I (Wittchen et al., 1997). Additionally, HC scored below cut-offs for clinically remarkable depressive symptoms ('S3-Leitlinie / Nationale VersorgungsLeitlinie Unipolare Depression Langfassung', 2015) on the BDI (Beck & Steer, 1987) and the HDRS (Hamilton, 1960) at all three time points. For detailed sample characteristics, see Table 1/online Supplementary Table S1.

### Electroconvulsive therapy

All patients in the ECT group stayed at inpatient treatment during the whole ECT series. Using the Thymatron IV system (Somatics Inc., Lake Bluff, IL), brief pulse ECT was conducted two or three times a week. Starting with nine to twelve sessions of ECT, sessions were continued if patients did not experience symptom relief. While electrode placement in one patient was not recorded, the other 16 patients in the ECT group initially received right unilateral ECT. In two patients, ECT treatment was switched to bilateral ECT as unilateral treatment failed to achieve sufficient symptom improvement. For details regarding ECT parameters, see online Supplementary Table S2.

### Structural MRI data acquisition and preprocessing

Structural data of all participants were obtained using a research-dedicated 3-Tesla-MRI ('Gyrosan Intera 3 T' Philips Medical Systems, Best, NL). For data acquisition and MRI parameters, see online Supplementary Method S1. Structural images were pre-processed longitudinally using the CAT12-toolbox (version 12.7 [revision1615], <http://www.neuro.uni-jena.de/cat12-html/cat.html>). Images were intra-subject rigid registered and bias-corrected, tissue classified, and normalized to MNI-space using linear (12-parameter affine) and non-linear transformations including high-dimensional normalization using Shooting-Registration. Gray matter segments were modulated by non-linear components only to preserve actual GM values locally (modulated GM volumes). The modulated gray matter images were smoothed with a Gaussian kernel of 8 mm full width half maximum.

### Statistical analysis

Demographic and clinical data were analyzed using SPSS Statistics (Version 25.0; IBM Corporation). A  $3 \times 3$  ANOVA with group (ECT v. TAU v. HC) as between-subjects factor and time ( $t_0$  v.  $t_1$  v.  $t_2$ ) as within-subjects factor was performed on HDRS and BDI scores.

Structural brain data were analyzed on whole-brain level using statistical parametric mapping software (SPM12, version 7771, Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) with a conservative family-wise error (FWE)-corrected threshold of  $p_{FWE} < 0.05$  on the voxel-level and a cluster size threshold of  $k \geq 100$ . Age, sex, medication load index and total intracranial volume were included as covariates of no interest. We conducted a  $3 \times 3$  ANOVA with group (ECT, TAU, HC) as between-subjects factor and time ( $t_0$ ,  $t_1$ ,  $t_2$ ) as within-subjects factor in SPM12. In an additional  $3 \times 3$  ANOVA, the HDRS score was included as a covariate of no interest to account for depression severity.

To investigate if GMV changes within the ECT group were associated with clinical outcome, GMV was extracted at  $t_0$ ,  $t_1$  and  $t_2$  from clusters showing a significant GMV increase ( $t_0$  v.  $t_1$ ) in a repeated-measures ANOVA (Fig. 1/online Supplementary

Table S3).  $\Delta\text{GMV}_{\text{post-baseline}}$  (GMV post – GMV baseline) and  $\Delta\text{GMV}_{\text{follow-up-post}}$  (GMV follow-up – GMV post) were calculated in SPSS Statistics (Version 25.0; IBM Corporation) for each patient, representing changes between  $t_0$  and  $t_1$ , and between  $t_1$  and  $t_2$ , respectively. Besides, HDRS and BDI score changes were calculated reflecting immediate ( $t_0$  v.  $t_1$ ), delayed ( $t_0$  v.  $t_2$ ) and long-term ( $t_1$  v.  $t_2$ ) clinical outcome. Thereby, higher change scores implicated symptom increase. Spearman's correlation coefficient was used to examine associations of short-term  $\Delta\text{GMV}_{\text{post-baseline}}$  changes with immediate or delayed clinical outcome, and of long-term  $\Delta\text{GMV}_{\text{follow-up-post}}$  changes with long-term clinical outcome. For details on the correlation analyses of  $\Delta\text{GMV}$  changes with changes in specific depressive symptoms (suicidality and delusion), see online Supplementary Method S2.

## Results

### Clinical response

HDRS and BDI scores significantly decreased within both MDD groups from  $t_0$  to  $t_1$  ( $M_{\text{Diff-ECT}} = 14.118$ ,  $M_{\text{Diff-TAU}} = 10.879$ ; both  $p < 0.001$ ) indicating treatment efficacy (online Supplementary Result S1). According to the definition of at least 50% decrease on the HDRS total score from  $t_0$  to  $t_1$ , there were 58.8% ( $n = 10$ ) responders and 41.2% ( $n = 7$ ) non-responders to ECT. The number of ECT sessions did not correlate with the clinical response (both  $p \geq 0.818$ ). Within the TAU group, there were 48.5% ( $n = 16$ ) responders and 51.5% ( $n = 17$ ) non-responders. There was no significant difference in response rates between MDD groups ( $\chi^2_{(1)} = 0.480$ ,  $p = 0.488$ ). For details on ECT treatments between  $t_1$  and  $t_2$  in responder groups, see online Supplementary Fig. S2.

### Longitudinal effects of ECT on gray matter volume

The  $3 \times 3$  ANOVA yielded a significant group  $\times$  time interaction ( $p_{FWE} < 0.001$ ,  $\eta_p^2 = 0.249$ – $0.499$ ) resulting from significant GMV increases from  $t_0$  to  $t_1$  ( $p_{FWE} < 0.001$ ,  $\eta_p^2 = 0.376$ – $0.848$ ) and significant GMV decreases from  $t_1$  to  $t_2$  ( $p_{FWE} < 0.001$ ,  $\eta_p^2 = 0.627$ – $0.934$ ) in the ECT group in clusters comprising the hippocampus, amygdala, inferior frontal gyrus and insula (Table 2/Fig. 2/online Supplementary Table S4). No significant changes in GMV were found in the TAU group and the HC group from  $t_0$  to  $t_1$  or from  $t_1$  to  $t_2$ . With a more lenient cluster threshold ( $k < 100$ ), minor GMV decreases from  $t_1$  to  $t_2$  were also evident in both control groups. There was no significant main effect of group in clusters  $k \geq 100$ . With a more lenient statistical threshold of  $p_{unc} < 0.001$ , a significant main effect of group could be found ( $p_{unc} < 0.001$ ,  $\eta_p^2 = 0.140$ – $0.227$ ; online Supplementary Table S5). For exploratory association analyses between short-term and long-term GMV changes in the ECT group, see online Supplementary Result S2. Under inclusion of the HDRS score as a covariate of no interest in the  $3 \times 3$  ANOVA to account for depression severity, the group  $\times$  time interaction and the respective post-hoc  $t$  tests within the ECT group remained significant (online Supplementary Table S6).

### Associations of gray matter volume change with clinical outcome in the ECT group

Short-term  $\text{GMV}_{\text{post-baseline}}$  increase in clusters comprising subcortical structures such as the hippocampus and amygdala correlated with an immediate (all  $p \leq 0.049$ ) and delayed depressive symptom

**Table 1.** Sample characteristics

|                                                                                                                        | ECT group<br><i>n</i> = 17 | TAU group<br><i>n</i> = 33 | HC group<br><i>n</i> = 21 | <i>p</i> value <sup>a</sup> | <i>p</i> value <sup>b</sup> |
|------------------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------|---------------------------|-----------------------------|-----------------------------|
|                                                                                                                        | Mean (s.d.)                | Mean (s.d.)                | Mean (s.d.)               |                             |                             |
| Sociodemographic characteristics                                                                                       |                            |                            |                           |                             |                             |
| Age at <i>t</i> <sub>0</sub> (years)                                                                                   | 47.47 (10.94)              | 36.12 (11.70)              | 40.57 (12.98)             | 0.009                       | 0.002                       |
| Sex (m/f) <sup>c</sup>                                                                                                 | 8/9                        | 16/17                      | 10/11                     | 0.995                       | 0.924                       |
| Time between <i>t</i> <sub>0</sub> and <i>t</i> <sub>1</sub> measurement (weeks)                                       | 7.22 (3.80)                | 6.77 (1.34)                | 8.69 (2.90)               | 0.032                       | 0.539                       |
| Time between <i>t</i> <sub>0</sub> and <i>t</i> <sub>2</sub> measurement (years)                                       | 2.17 (0.23)                | 2.23 (0.30)                | 2.11 (0.24)               | 0.262                       | 0.477                       |
| Symptom severity                                                                                                       |                            |                            |                           |                             |                             |
| HDRS <i>t</i> <sub>0</sub>                                                                                             | 25.18 (3.91)               | 23.06 (4.36)               | 0.81 (1.63)               | <0.001                      | 0.099                       |
| HDRS <i>t</i> <sub>1</sub>                                                                                             | 11.06 (6.64)               | 12.18 (8.27)               | 0.95 (1.40)               | <0.001                      | 0.630                       |
| HDRS <i>t</i> <sub>2</sub>                                                                                             | 12.06 (9.48)               | 10.42 (8.60)               | 1.29 (1.68)               | <0.001                      | 0.542                       |
| BDI <i>t</i> <sub>0</sub> <sup>d</sup>                                                                                 | 32.12 (8.77)               | 26.42 (8.93)               | 2.80 (3.05)               | <0.001                      | 0.039                       |
| BDI <i>t</i> <sub>1</sub> <sup>e</sup>                                                                                 | 19.88 (11.51)              | 16.48 (10.31)              | 1.45 (2.67)               | <0.001                      | 0.310                       |
| BDI <i>t</i> <sub>2</sub> <sup>f</sup>                                                                                 | 19.56 (12.98)              | 14.94 (11.54)              | 2.15 (3.00)               | <0.001                      | 0.218                       |
| Clinical characteristics at baseline                                                                                   |                            |                            |                           |                             |                             |
| Age of Onset <sup>g</sup>                                                                                              | 31.96 (15.55)              | 27.86 (11.34)              | –                         | –                           | 0.308                       |
| No. of depressive episodes before <i>t</i> <sub>0</sub>                                                                | 6.88 (7.42)                | 4.76 (7.62)                | –                         | –                           | 0.351                       |
| Cumulative duration of depressive state before <i>t</i> <sub>0</sub> (months)                                          | 43.65 (35.06)              | 21.12 (21.43)              | –                         | –                           | 0.007                       |
| No. of inpatient treatments before <i>t</i> <sub>0</sub>                                                               | 3.76 (2.14)                | 2.00 (1.48)                | –                         | –                           | 0.001                       |
| Cumulative duration of inpatient treatment before <i>t</i> <sub>0</sub> (months) <sup>h</sup>                          | 6.63 (4.24)                | 2.35 (3.59)                | –                         | –                           | 0.001                       |
| Clinical characteristics at follow-up                                                                                  |                            |                            |                           |                             |                             |
| No. of depressive episodes between <i>t</i> <sub>0</sub> & <i>t</i> <sub>2</sub>                                       | 0.88 (0.78)                | 0.85 (0.94)                | –                         | –                           | 0.899                       |
| Relapse (no/yes), No. of patients between <i>t</i> <sub>0</sub> & <i>t</i> <sub>2</sub> <sup>c</sup>                   | 5/12                       | 14/19                      | –                         | –                           | –                           |
| No. of inpatient treatments between <i>t</i> <sub>0</sub> & <i>t</i> <sub>2</sub>                                      | 0.53 (0.72)                | 0.24 (0.56)                | –                         | –                           | 0.126                       |
| No. of outpatient psychiatric visits between <i>t</i> <sub>0</sub> & <i>t</i> <sub>2</sub> <sup>i</sup>                | 9.47 (10.13)               | 12.53 (20.92)              | –                         | –                           | 0.573                       |
| No. of outpatient psychotherapeutic visits between <i>t</i> <sub>0</sub> & <i>t</i> <sub>2</sub> <sup>j</sup>          | 23.76 (28.35)              | 38.72 (54.51)              | –                         | –                           | 0.300                       |
| Remission status (no remission/ partial and full remission), No. of patients at <i>t</i> <sub>2</sub> <sup>c</sup>     | 7/10                       | 10/23                      | –                         | –                           | –                           |
| Duration of remission between <i>t</i> <sub>0</sub> & <i>t</i> <sub>2</sub> in remitted patients (months) <sup>k</sup> | 5.89 (7.72)                | 12.26 (9.39)               | –                         | –                           | 0.089                       |
| Comorbidity                                                                                                            |                            |                            |                           |                             |                             |
| Acute comorbidity (yes/no), No. of patients <sup>c</sup> at <i>t</i> <sub>0</sub>                                      | 5/12                       | 13/20                      | –                         | –                           | 0.486                       |
| Acute comorbidity (yes/no), No. of patients <sup>c</sup> at <i>t</i> <sub>2</sub>                                      | 8/9                        | 11/22                      | –                         | –                           | 0.344                       |
| Psychopharmacological treatment <sup>l</sup>                                                                           |                            |                            |                           |                             |                             |
| Medication load index at <i>t</i> <sub>0</sub>                                                                         | 4.06 (1.78)                | 2.12 (0.96)                | –                         | –                           | <0.001                      |
| Medication load index at <i>t</i> <sub>1</sub>                                                                         | 4.41 (2.06)                | 2.70 (1.36)                | –                         | –                           | 0.001                       |
| Medication load index at <i>t</i> <sub>2</sub>                                                                         | 4.88 (2.60)                | 1.39 (1.44)                | –                         | –                           | <0.001                      |

ECT, electroconvulsive therapy; TAU, treatment as usual; HC, healthy controls; HDRS, Hamilton depression rating scale; BDI, Beck depression inventory.

<sup>a</sup>Comparing patients from the ECT, the TAU and the HC group by using an one-way analysis of variance except where noted.

<sup>b</sup>Comparing patients from the ECT and the TAU group by using an unpaired two-tailed *t* test except where noted.

<sup>c</sup>*p* values were obtained using the  $\chi^2$ -test.

<sup>d</sup>Information was missing for *n* = 2 in the TAU and *n* = 1 in the HC group.

<sup>e</sup>Information was missing for *n* = 1 in the ECT, *n* = 2 in the TAU and *n* = 1 in the HC group.

<sup>f</sup>Information was missing for *n* = 1 in the ECT, *n* = 2 in the TAU and *n* = 1 in the HC group.

<sup>g</sup>Information was missing for *n* = 2 in the ECT group.

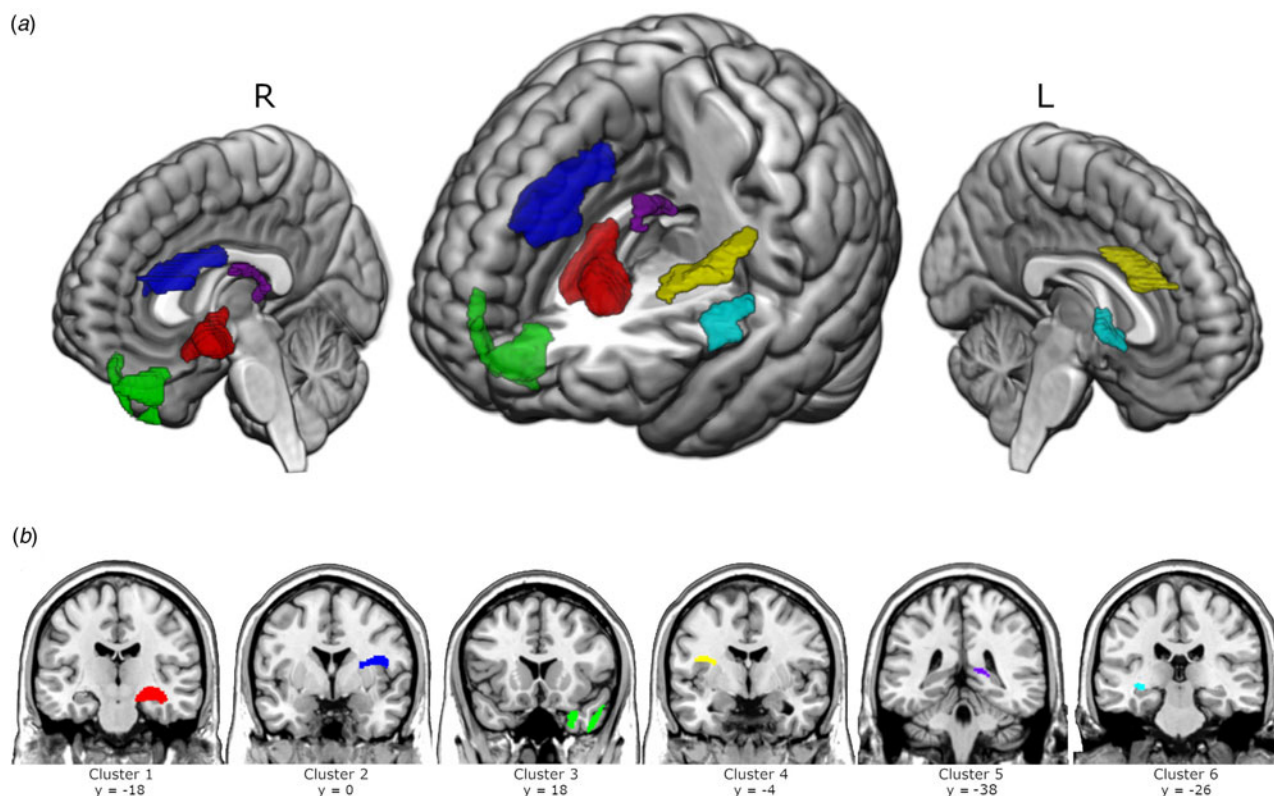
<sup>h</sup>Information was missing for *n* = 1 in the ECT and *n* = 2 in the TAU group.

<sup>i</sup>Information was missing for *n* = 1 in the TAU group.

<sup>j</sup>Information was missing for *n* = 4 in the TAU group.

<sup>k</sup>Information was missing for *n* = 1 in the ECT and *n* = 4 in the TAU group.

<sup>l</sup>Detailed information on psychopharmacological treatment can be found in online Supplementary Table S1.



**Figure 1.** Graphical illustration of extracted clusters for the association analyses in the ECT group. Gray matter volume at  $t_0$ ,  $t_1$  and  $t_2$  in clusters showing a significant gray matter volume increase from  $t_0$  to  $t_1$  in the repeated-measures ANOVA in the ECT group were extracted. (a) 3D render of the brain with extracted clusters. (b) Sagittal view of the extracted clusters at y-coordinates. Different colors indicate different clusters: Red = Cluster 1 (Right hippocampus/ parahippocampal gyrus (g.)/ amygdala/ laterale geniculate nucleus/ pars reticula/ pallidum), Blue = Cluster 2 (Right insula/ rolandic operculum/ putamen/ inferior frontal g.), Green = Cluster 3 (Right middle temporal pole/ superior temporal pole/ parahippocampal g./ inferior temporal g./ posterior orbitofrontal cortex/ fusiform g.), Yellow = Cluster 4 (Left insula/ rolandic operculum/ inferior frontal g. putamen/ precentral g.), Violet = Cluster 5 (Right hippocampus/ posterior cingulate cortex/ medial pulvinar nucleus/ precuneus/ lateral pulvinar nucleus), Cyan = Cluster 6 (Left hippocampus/ laterale geniculate nucleus).

increase, i.e., a worsening of depressive symptoms (all  $p \leq 0.037$ , Table 3). Furthermore, long-term  $GMV_{\text{follow-up-post}}$  change correlated with BDI score change and number of depressive episodes between  $t_1$  and  $t_2$  (all  $p \leq 0.039$ , Table 3) indicating that more GMV loss over 2 years was associated with a worse long-term outcome in the ECT group. For correlation analyses with the number of ECT sessions and short-term  $\Delta GMV_{\text{post-baseline}}$  changes as covariates, see online Supplementary Table S7. Additional correlation analyses of  $\Delta GMV$  changes with changes in suicidality and delusion can be found in online Supplementary Result S3 and Supplementary Table S8.

## Discussion

Strengthening previous findings, our results reveal that GMV in regions with initial ECT-induced GMV increase decline over the course of 2 years after ECT. No such effects were observed in control groups. Short-term GMV increase correlated with immediate and delayed symptom increase, while long-term GMV decrease correlated with poor long-term depressive outcome.

### Long-term ECT-related structural changes and associations with clinical outcome

Our results extend previous findings by suggesting that GMV increases following ECT are temporary, as GMV significantly

decreases over 2 years in the ECT group. These changes were also evident when controlling for depression severity. No such changes were observed in control groups. Exploratory correlation analyses in the ECT group revealed that those with the largest short-term GMV increase had the strongest long-term GMV decline. Thereby, we observed global GMV increases following ECT, followed by global GMV decreases in the same areas 2 years later. Our results align with previous studies (Bouckaert et al., 2016; Gbyl et al., 2021, 2019; Nordanskog et al., 2014) showing that GMV returns to baseline values at  $t_2$  in the ECT group. In contrast, the TAU group showed no significant short-term GMV increases and hence no pronounced GMV loss over 2 years. However, minor GMV decreases from  $t_1$  to  $t_2$  were observed in the TAU and the HC group with a more lenient cluster threshold, indicating common effects of time and disease progression. Nordanskog et al. (2014) suggested that ECT may have led to an increased cell proliferation and the pronounced long-term GMV decrease therefore may be due to neuronal pruning and migration mechanisms. Neuronal pruning and migration processes could indicate that GMV loss in the long-term must not necessarily mean a worsening of depressive symptoms, as reported in previous studies (Bouckaert et al., 2016; Gbyl et al., 2019; Nordanskog et al., 2014). Although the link of GMV decreases following ECT with long-term clinical outcome was not investigated in these studies.

**Table 2.** Results of the group  $\times$  time interaction

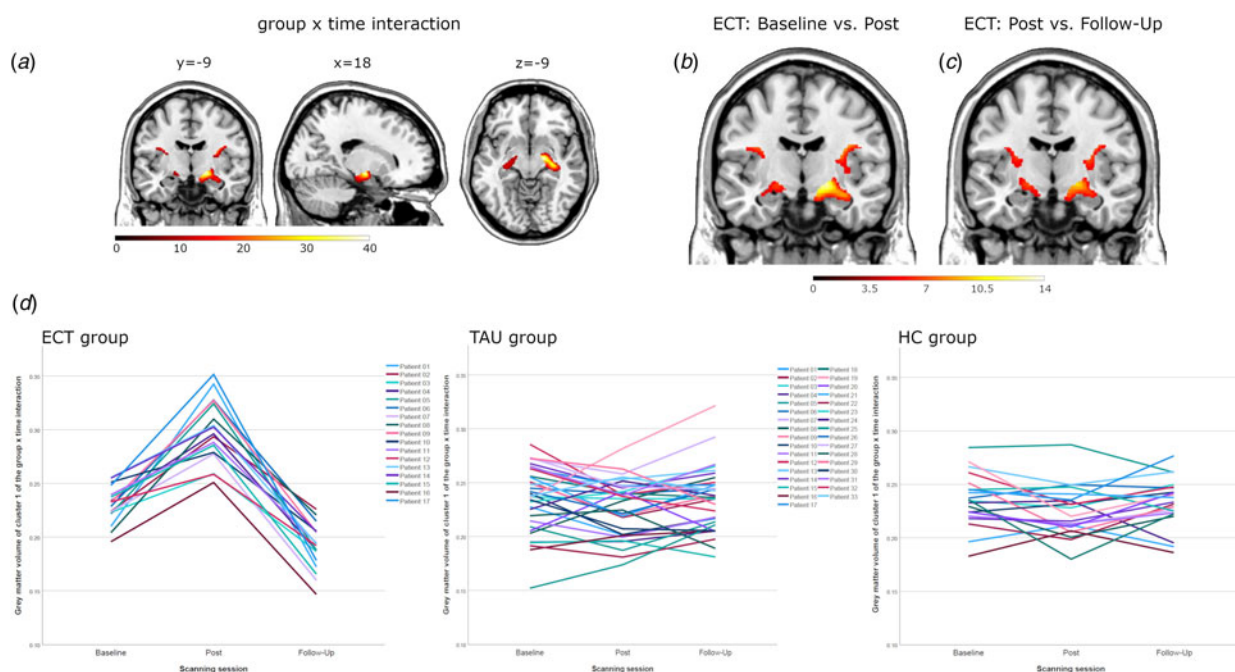
|                                                                                                                                  |      |                           | Peak voxel coordinates |     |     |                 |                        |                             |
|----------------------------------------------------------------------------------------------------------------------------------|------|---------------------------|------------------------|-----|-----|-----------------|------------------------|-----------------------------|
|                                                                                                                                  |      |                           | x                      | y   | z   |                 |                        |                             |
| Anatomical region <sup>a</sup>                                                                                                   | Side | Cluster size <sup>b</sup> | x                      | y   | z   | Test statistics |                        |                             |
| Group × time interaction effect <sup>c</sup>                                                                                     |      |                           |                        |     |     | F value         | p <sub>FWE</sub> value | η <sub>p</sub> <sup>2</sup> |
| Hippocampus/ amygdala/ lateral geniculate nucleus/ pallidum/ parahippocampal gyrus/ pars reticula                                | R    | 1303                      | 18                     | −9  | −9  | 39.03           | <0.001                 | 0.499                       |
| Putamen/ insula/ rolandic operculum/ inferior frontal gyrus                                                                      | R    | 883                       | 30                     | −2  | 16  | 33.54           | <0.001                 | 0.363                       |
| Insula/ putamen/ rolandic operculum/ inferior frontal gyrus                                                                      | L    | 330                       | −34                    | −8  | 20  | 15.69           | <0.001                 | 0.249                       |
| Hippocampus/ lateral geniculate nucleus                                                                                          | L    | 251                       | −30                    | −22 | −6  | 14.38           | <0.001                 | 0.274                       |
| Post-hoc tests <sup>d</sup> from baseline to post                                                                                |      |                           |                        |     |     | T value         | p <sub>FWE</sub> value | η <sub>p</sub> <sup>2</sup> |
| ECT group: Baseline < Post                                                                                                       |      |                           |                        |     |     |                 |                        |                             |
| Hippocampus/ parahippocampal gyrus/ amygdala/ pallidum/ lateral geniculate nucleus/ pars reticula                                | R    | 2066                      | 18                     | −9  | −9  | 13.09           | <0.001                 | 0.848                       |
| Putamen/ Insula/ rolandic operculum/ inferior frontal gyrus/ supramarginal gyrus                                                 | R    | 1708                      | 30                     | −2  | 16  | 11.49           | <0.001                 | 0.715                       |
| Insula/ rolandic operculum/ putamen/ inferior frontal gyrus/ precentral gyrus                                                    | L    | 820                       | −28                    | 0   | 16  | 8.11            | <0.001                 | 0.558                       |
| Hippocampus/ medial pulvinar nucleus/ posterior cingulate cortex/ precuneus/ lateral pulvinar nucleus/ anterior pulvinar nucleus | R    | 379                       | 9                      | −22 | 20  | 7.45            | <0.001                 | 0.602                       |
| Hippocampus/ lateral geniculate nucleus/ amygdala/ pallidum                                                                      | L    | 648                       | −28                    | −20 | −9  | 7.29            | <0.001                 | 0.376                       |
| Superior temporal pole/ middle temporal pole/ parahippocampal gyrus/ orbitofrontal cortex                                        | R    | 864                       | 30                     | 18  | −30 | 6.62            | <0.001                 | 0.786                       |
| Caudate nucleus                                                                                                                  | R    | 165                       | 12                     | 0   | 24  | 6.37            | <0.001                 | 0.489                       |
| TAU group: Baseline < Post                                                                                                       | −    | −                         | −                      | −   | −   | −               | N.S.                   | −                           |
| HC group: Baseline > Post                                                                                                        | −    | −                         | −                      | −   | −   | −               | N.S.                   | −                           |
| Post-hoc tests <sup>d</sup> from post to follow-up                                                                               |      |                           |                        |     |     | T value         | p <sub>FWE</sub> value | η <sub>p</sub> <sup>2</sup> |
| ECT group: Post > Follow-up                                                                                                      |      |                           |                        |     |     |                 |                        |                             |
| Hippocampus/ parahippocampal gyrus/ amygdala/ pallidum/ lateral geniculate nucleus/ superior temporal pole/ pars reticula        | R    | 1293                      | 20                     | −10 | −8  | 9.88            | <0.001                 | 0.934                       |
| Putamen/ insula/ rolandic operculum/ inferior frontal gyrus                                                                      | R    | 911                       | 30                     | −2  | 16  | 9.78            | <0.001                 | 0.871                       |
| Putamen/ insula/ hippocampus/ pallidum/ laterale geniculate nucleus/ rolandic operculum/ amygdala                                | L    | 1039                      | −28                    | −4  | 16  | 7.70            | <0.001                 | 0.816                       |
| Caudate nucleus                                                                                                                  | R    | 263                       | 10                     | 2   | 21  | 6.48            | <0.001                 | 0.627                       |
| TAU group: Post > Follow-up                                                                                                      | −    | −                         | −                      | −   | −   | −               | N.S.                   | −                           |
| HC group: Post > Follow-up                                                                                                       | −    | −                         | −                      | −   | −   | −               | N.S.                   | −                           |
| Post-hoc tests <sup>d</sup> from baseline to follow-up                                                                           |      |                           |                        |     |     | T value         | p <sub>FWE</sub> value | η <sub>p</sub> <sup>2</sup> |
| ECT group: Baseline < Follow-up                                                                                                  |      |                           |                        |     |     |                 |                        |                             |
| TAU group: Baseline > Follow-up                                                                                                  |      |                           |                        |     |     |                 |                        |                             |
| HC group: Baseline > Follow-up                                                                                                   |      |                           |                        |     |     |                 |                        |                             |

ECT, electroconvulsive therapy; TAU, treatment as usual; HC, healthy controls.

<sup>a</sup>Detailed information on percentages of brain areas in significant clusters can be found in online Supplementary Table S4.<sup>b</sup>Only significant clusters ( $p_{FWE} < 0.050$ ) with cluster size  $k \geq 100$  are reported.<sup>c</sup> $df_1 = 4$ ;  $df_2 = 200$ .<sup>d</sup> $df = 200$ .

Our correlational findings, in contrast, highlight the relevant interplay of GMV decrease with long-term depressive symptomatology – even if ECT-induced GMV increases have occurred

beforehand and were controlled for in the analyses. GMV loss was associated with a worsening of depressive symptoms and with a higher number of depressive episodes in the 2-year



**Figure 2.** Longitudinal effects of ECT on gray matter volume. (a) Visualization of the longitudinal group  $\times$  time interaction of the whole-brain analysis ( $x=18$ ,  $y=-9$ ,  $z=-9$ ; all  $p_{FWE} < 0.001$ ) on a MNI Template, driven by (b) significant GMV increases from  $t_0$  to  $t_1$  ( $y=-10$ ,  $p_{FWE} < 0.001$ ) and (c) significant GMV decreases from  $t_1$  to  $t_2$  ( $y=-10$ ,  $p_{FWE} < 0.001$ ) in the ECT group. Bar indicates (a)  $F$  values and (b) and (c)  $t$  values. (d) Visualization of the individual time course of gray matter volume changes (in mm<sup>3</sup>) of the first significant cluster of the group  $\times$  time interaction ( $k=1303$ ,  $x=18$ ,  $y=-9$ ,  $z=-9$ ), separately for each group for the three scanning sessions. ECT, Electroconvulsive therapy; TAU, Treatment as usual; HC, Healthy controls.

interval. This is consistent with previous studies linking structural abnormalities of brain areas such as the hippocampus (Cattarinussi, Delvecchio, Maggioni, Bressi, & Brambilla, 2021; Frodl et al., 2008; Schmaal et al., 2016; Videbech & Ravnkilde, 2004), amygdala (Cattarinussi et al., 2021), insula (Soriano-Mas et al., 2011; Stratmann et al., 2014; Zaremba et al., 2018a) and pre-frontal cortex (Frodl et al., 2008; Schmaal et al., 2016; Zaremba et al., 2018a) to an unfavorable disease progression (e.g. greater number of relapses) in depression (Frodl et al., 2008; Soriano-Mas et al., 2011; Stratmann et al., 2014; Videbech & Ravnkilde, 2004; Zaremba et al., 2018a, 2018b). Our study thus highlights potential dysfunctions within the fronto-limbic circuitry, consistent with neurobiological models of depression that propose a bottom-up emotional processing bias and a disruption of top-down functions (Mayberg et al., 1999; Zaremba et al., 2018a). Our findings may suggest that the effect of disease progression on brain structure, possibly in line with the neurotoxicity hypothesis of depression (Sapolsky, 2000), or conversely, the effect of a constitutional dysfunction in plasticity processes (Nordanskog et al., 2014) on disease progression continues to play a major role even after ECT and related GMV increases. Interestingly, the TAU group showed no pronounced long-term GMV loss, despite disease progression being expected to have an effect. Thus, the negative association between long-term GMV loss and clinical outcome may be related to ECT and reflect the transient nature of ECT-induced effects.

In terms of practical implications, a worsening of depressive symptoms and therewith, GMV loss should be prevented. First evidence demonstrated the effectiveness of continuation ECT in sustaining the antidepressant effect in ECT responder (Kellner et al., 2016), though our subgroups of ECT responders were too small for such extended analysis. Future research that investigates

the effect of continuation ECT on brain structure and its relevance for clinical outcome is strongly needed. Furthermore, invasive vagus nerve stimulation (VNS) was shown to induce hippocampal GMV increases (Perini et al., 2017) and to reduce the need of maintenance ECT (Aaronson et al., 2021). Hypothetically, VNS in ECT patients might prevent GMV decrease in the long-term after ECT series. The efficacy of other treatment options following ECT such as cognitive-behavioral therapy (CBT) might also be relevant to investigate, as acute CBT was found to be effective in preventing relapse (Fournier et al., 2022). Moreover, although widely discussed, studies investigating the long-term persistence of other neurobiological changes following an ECT series such as HPA-axis activity changes are still missing.

#### Short-term ECT-related structural changes and associations with clinical outcome

In accordance with previous imaging studies (Enneking et al., 2019), our findings revealed notable GMV increases after ECT, e.g., in the hippocampus-amygdala complex, even when controlling for depression severity. As no significant GMV changes were found in the TAU and HC group, GMV increases in the ECT group seem to be attributable to the effect of ECT instead of depression, medication or time. Neuroplasticity processes such as cell proliferation and neurogenesis are discussed to be potential mediators of ECT-related structural changes (Enneking et al., 2019). However, the notable GMV increases could potentially also mirror decreases in white matter (WM), particularly in regions characterized by close proximity of diverse tissue types. This could be attributed to the complementary relationship between GM and WM values. In line with this, previous diffusion tensor imaging studies have delineated alterations in WM

**Table 3.** Associations<sup>a</sup> of gray matter volume changes with clinical outcome measures

| $\Delta$ GMV changes                                                          | $\Delta$ HDRS score change |                             | $\Delta$ BDI score change <sup>b</sup> |                             | Number of depressive episodes |               |
|-------------------------------------------------------------------------------|----------------------------|-----------------------------|----------------------------------------|-----------------------------|-------------------------------|---------------|
|                                                                               | <i>r</i>                   | <i>p</i>                    | <i>r</i>                               | <i>p</i>                    | <i>r</i>                      | <i>p</i>      |
| Short-term gray matter volume change and immediate clinical outcome variables |                            |                             |                                        |                             |                               |               |
| $t_0$ v. $t_1$                                                                | $t_0$ v. $t_1$             |                             | $t_0$ v. $t_1$                         |                             | –                             |               |
| Cluster 1                                                                     | <b>0.484</b>               | <b>0.049*</b>               | 0.080                                  | 0.770                       | –                             | –             |
| Cluster 2                                                                     | <b>0.585</b>               | <b>0.014**<sup>c</sup></b>  | 0.038                                  | 0.888                       | –                             | –             |
| Cluster 3                                                                     | 0.160                      | 0.540                       | –0.112                                 | 0.680                       | –                             | –             |
| Cluster 4                                                                     | <b>0.565</b>               | <b>0.018*</b>               | 0.290                                  | 0.276                       | –                             | –             |
| Cluster 5                                                                     | 0.111                      | 0.672                       | –0.305                                 | 0.251                       | –                             | –             |
| Cluster 6                                                                     | 0.290                      | 0.258                       | 0.479                                  | 0.061                       | –                             | –             |
| Short-term gray matter volume change and delayed clinical outcome variables   |                            |                             |                                        |                             |                               |               |
| $t_0$ v. $t_1$                                                                | $t_0$ v. $t_2$             |                             | $t_0$ v. $t_2$                         |                             | $t_0$ v. $t_2$                |               |
| Cluster 1                                                                     | 0.389                      | 0.122                       | 0.213                                  | 0.427                       | 0.404                         | 0.108         |
| Cluster 2                                                                     | <b>0.609</b>               | <b>0.009***<sup>c</sup></b> | 0.365                                  | 0.165                       | 0.450                         | 0.070         |
| Cluster 3                                                                     | 0.016                      | 0.951                       | 0.128                                  | 0.637                       | –0.251                        | 0.331         |
| Cluster 4                                                                     | <b>0.509</b>               | <b>0.037*</b>               | <b>0.533</b>                           | <b>0.034*</b>               | <b>0.496</b>                  | <b>0.043*</b> |
| Cluster 5                                                                     | 0.167                      | 0.522                       | –0.029                                 | 0.914                       | 0.247                         | 0.340         |
| Cluster 6                                                                     | 0.252                      | 0.329                       | <b>0.620</b>                           | <b>0.010**<sup>c</sup></b>  | 0.081                         | 0.758         |
| Long-term gray matter volume change and long-term clinical outcome variables  |                            |                             |                                        |                             |                               |               |
| $t_1$ v. $t_2$                                                                | $t_1$ v. $t_2$             |                             | $t_1$ v. $t_2$                         |                             | $t_1$ v. $t_2$                |               |
| Cluster 1                                                                     | –0.143                     | 0.585                       | <b>–0.579</b>                          | <b>0.024*</b>               | –0.433                        | 0.082         |
| Cluster 2                                                                     | –0.348                     | 0.171                       | <b>–0.657</b>                          | <b>0.008***<sup>c</sup></b> | <b>–0.535</b>                 | <b>0.027*</b> |
| Cluster 3                                                                     | –0.130                     | 0.618                       | –0.429                                 | 0.111                       | 0.141                         | 0.590         |
| Cluster 4                                                                     | –0.230                     | 0.375                       | –0.355                                 | 0.194                       | –0.450                        | 0.070         |
| Cluster 5                                                                     | –0.036                     | 0.892                       | <b>–0.536</b>                          | <b>0.039*</b>               | –0.415                        | 0.097         |
| Cluster 6                                                                     | –0.247                     | 0.339                       | –0.280                                 | 0.312                       | –0.318                        | 0.214         |

GMV, gray matter volume; HDRS, Hamilton depression rating scale; BDI, Beck depression inventory.

<sup>a</sup>Correlation analyses using Spearman's correlation coefficient.

<sup>b</sup>Information regarding BDI score change was missing for  $n = 1$  patient in the ECT group.

<sup>c</sup>No correction for multiple comparisons was made. With a Bonferroni-adjusted  $p$ -value of 0.016, only these correlation results remain significant.

\* $p < 0.05$ , \*\*  $p < 0.01$

microstructure (Gryglewski et al., 2020; Lyden et al., 2014; Nobuhara et al., 2004; Repple et al., 2020). It should be noted, however, that the majority of results of these studies (Gryglewski et al., 2020; Lyden et al., 2014; Nobuhara et al., 2004) suggests that ECT leads to an increase rather than a decrease in WM integrity in structures such as limbic and frontal regions. Moreover, a recent multi-center study (Ousdal et al., 2020) supported this idea by showing that there were no significant changes in WM volume following ECT, thereby attenuating the aforementioned interpretation.

Besides, it is still questionable whether GMV increases account for the antidepressant effect of ECT (Sackeim, 2020). In line with two studies (Gyger et al., 2021; Olteidal et al., 2018), the present study indicated that patients with a greater GMV increase after ECT showed less immediate symptom improvement. Moreover, GMV increases were also positively associated with clinical outcome after 2 years indicating less GMV increase in those with

delayed symptom improvement. Nordanskog et al. (Nordanskog et al., 2014) suggested a modulating effect of the number of ECT sessions. Interestingly, our results remained significant when controlling for the number of ECT sessions. Additionally, the number of ECT sessions was not correlated with clinical outcome. However, larger, well powered studies like the multi-center study by Olteidal and colleagues (Olteidal et al., 2018), strongly support the assumption that ECT parameters, such as the number of sessions, exert a modulating effect on the extent of GMV changes. Previous studies (Mulders et al., 2020; Olteidal et al., 2018; Ousdal et al., 2020) also emphasize the relevance of electrode placement, which appears to play a role in the lateralization of GMV changes. The dose-dependent effect suggests that the GMV change following ECT may be a biological correlate of the electric seizures themselves, essentially an epiphenomenon of ECT, rather than underlying the antidepressant effect. In our study, the observed inconsistency may be due to a low statistical

power. Instead, other neurobiological mechanisms such as ECT-induced alterations, e.g., in connectivity (Takamiya et al., 2020), neurotransmission or inflammatory processes (Stippl, Kirkgoze, Bajbouj, & Grimm, 2020) might be responsible for the antidepressant effect. Drawing on Gyger and colleagues' interpretation of similar findings (Gyger et al., 2021), it could also be suggested that these associations arise due to the fact that patients with smaller pre-treatment GMV may be able to undergo larger GMV increases during ECT, but at the same time, may have a poorer prognosis and experience less improvements from the ECT treatment. Consequently, in the long term, such patients may display a decrease in GMV and a worsening of their symptoms, as showed in the 2-year interval of this study. Thus, while ECT-associated GMV increases do not seem to underlie the clinical response, GMV decreases in the naturalistic course of depression may be a correlate of an unfavorable disease progression, as stated by the neurotoxicity hypothesis and shown in prospective long-term neuroimaging studies (Zaremba et al., 2018a).

Consistent with previous studies included in the work by Fink and Taylor (2007), a significant decrease in suicidality and delusion was observed following ECT, which remained stable in the long-term course after ECT. However, in this study, no significant associations were found between GMV changes and these specific symptom improvements. Therefore, the results suggest that GMV increases after ECT are neither associated with general, nor with specific symptom improvement (as suicidality or psychotic features). In contrast, a recent mega-analysis by Cano and colleagues (Cano, Chowdhury, & Camprodon, 2023) found increases of the surface area of the rostral ACC to be associated with the anti-suicidal response following ECT. It is important to acknowledge our study's limitation in using only individual items from the HDRS for the sub-analysis. Consequently, the reliability of these individual items is limited. As psychotic features were rare in our sample, variance on the delusion subscale was restricted, limiting these correlation analyses as well.

### Strengths and limitations

Our study is the first to investigate ECT-induced structural changes in MDD in a naturalistic 2-year follow-up design with a TAU and HC group. The study provides high external validity and disentangles ECT-induced effects from those of time, medication and course of depression. By covering a time interval of 2 years, our study provides important evidence on the long-term transience of ECT-induced brain structural changes. The whole-brain approach allowed us, in contrast to many ROI-driven studies, to consider all clusters that actually changed during ECT. Despite these new and encouraging results, some limitations must be acknowledged. First, the sample sizes in the subgroups were relatively small, a known concern in multifaceted and time-consuming study designs with patient populations that are difficult to recruit (Jehna et al., 2020). Second, it is essential to consider that partial volume effects could represent a limitation, potentially impacting the accuracy of the results (e.g. clusters in Fig. 2). As these effects are inherent to the finite spatial resolution of the imaging modality, entire avoidance, particularly in modalities like MRI, is challenging. Nonetheless, given the proximity of different tissue types, particularly at GM/WM boundaries, cautious interpretation of the findings is advised in consideration of these effects. Third, we did not conduct a randomized clinical trial. It was evident that the ECT group had a more unfavorable course of depression before baseline and was classified as

treatment-resistant due to the lack of efficacy of antidepressant medication compared to the TAU group. It may have limited the comparability of the two patient groups. However, considering that both patient groups met the criteria for a diagnosis of moderate to severe MDD at baseline, were undergoing inpatient treatment due to MDD and did not differ in their HDRS scores, owing to the naturalistic design the comparability of the two patient groups was given. Furthermore, results of brain structural changes remained significant even after controlling for depression severity. Fourth, we have not investigated associations between symptom improvement and GMV changes in certain subfields of brain regions e.g., the anterior hippocampus (Nuninga et al., 2020). Such changes could map the underlying neurobiological mechanisms (Nuninga et al., 2020) more precisely. However, subfield segmentation requires very high-resolution scans (Nuninga et al., 2020). Fifth, future research should also consider closer follow-up intervals or ecological momentary assessment studies following ECT, to obtain more reliable data on disease progression and delayed treatment effects.

### Conclusion

Our results showed that ECT-induced GMV increases are transient, as GMV strongly decreased 2 years after ECT. Such GMV changes were not found in a healthy and MDD non-ECT control group. The association between GMV decreases and poor long-term outcome supports the transience of ECT-induced effects on structural and symptom level. Findings of notable GMV increases following ECT in areas that have been linked to the etiology and maintenance of MDD replicate immediate ECT-related effects found in previous studies. These GMV increases were associated with less immediate and delayed symptom improvement. Additionally, GMV changes were not found to be associated with changes in suicidality and delusion. Therefore, it remains elusive whether ECT-induced GMV increases are relevant for the antidepressant effect of ECT. The results seem to suggest that ECT-induced GMV increases are an epiphenomenon, while GMV decreases in the naturalistic long-term course of disease appear to be a correlate of relapse or ongoing depression, as stated by the neurotoxicity hypothesis.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291723002647>

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**Competing interest.** None.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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