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Influence of electroconvulsive therapy on white matter structure in a diffusion tensor imaging study

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Abstract

Background. Electroconvulsive therapy (ECT) is a fast-acting intervention for major depressive disorder. Previous studies indicated neurotrophic effects following ECT that might contribute to changes in white matter brain structure. We investigated the influence of ECT in a non-randomized prospective study focusing on white matter changes over time.

Methods. Twenty-nine severely depressed patients receiving ECT in addition to inpatient treatment, 69 severely depressed patients with inpatient treatment (NON-ECT) and 52 healthy controls (HC) took part in a non-randomized prospective study. Participants were scanned twice, approximately 6 weeks apart, using diffusion tensor imaging, applying tract-based spatial statistics. Additional correlational analyses were conducted in the ECT subsample to investigate the effects of seizure duration and therapeutic response.

Results. Mean diffusivity (MD) increased after ECT in the right hemisphere, which was an ECT-group-specific effect. Seizure duration was associated with decreased fractional anisotropy (FA) following ECT. Longitudinal changes in ECT were not associated with therapy response. However, within the ECT group only, baseline FA was positively and MD negatively associated with post-ECT symptomatology.

Conclusion. Our data suggest that ECT changes white matter integrity, possibly reflecting increased permeability of the blood–brain barrier, resulting in disturbed communication of fibers. Further, baseline diffusion metrics were associated with therapy response. Coherent fiber structure could be a prerequisite for a generalized seizure and inhibitory brain signaling necessary to successfully inhibit increased seizure activity.

Introduction

Major depressive disorder is a common, recurrent and costly disorder, with a life-time prevalence of roughly 16.6% (Kessler *et al*., 2005). Further, 15–33% of patients are classified as treatment resistant (Berlim *et al*., 2008), defined as two failed attempts to achieve significant clinical improvement with pharmacologically different antidepressants administered in adequate dose, duration and with compliance. For treatment-resistant patients, electroconvulsive therapy (ECT) is a valuable alternative as 60–80% improve and 50–60% achieve remission (Weiner and Reti, 2017). Understanding which patient might benefit from ECT independent of previous failed treatment attempts might therefore improve patient care.

ECT is a fast-acting intervention (Ottosson and Odeberg, 2012) with high response rates (Fink, 2014). In clinical practice, ECT response is linked to seizure quality parameters (Shah *et al*., 2013; Minelli *et al*., 2016). For instance, in current clinical application, ECT treatments with short seizure lengths below 25 s are considered insufficient.

The underlying mechanisms explaining the antidepressant effect of ECT remain uncertain (Hoy and Fitzgerald, 2010). On the one hand, ECT seems to normalize an immune system dissemblance and inflammatory processes associated with depression (Yrondi *et al*., 2017). On the other hand, studies point to neurotrophic effects such as enhanced neurogenesis (Madsen *et al*., 2000), angiogenesis (Hellsten *et al*., 2005), gliogenesis (Wennström *et al*., 2006), synaptogenesis and heightened axonal tropism (Nickl-Jockschat *et al*., 2016) after

ECT. This neurotrophic theory is supported both by animal (Malberg *et al.*, 2000; Kondratyev *et al.*, 2002) and human studies (Bumb *et al.*, 2015; Redlich *et al.*, 2016). These changes might influence white matter structure to an extent that could be measured by diffusion tensor imaging (DTI). This magnetic resonance imaging technique measures diffusion of water to quantify white matter integrity.

Nonetheless, only three DTI studies investigated ECT effects yielding inconsistent results. In a longitudinal study with late-life depressed patients, mean fractional anisotropy (FA), a measure often associated with fiber integrity, increased in selected regions of interest in frontal white matter in eight patients when studying at 1.5 Tesla (T) (Nobuhara *et al.*, 2004). Lyden *et al.* (2014) showed that FA increased after ECT in the anterior cingulum, forceps minor, and left superior longitudinal fasciculus when studying at 3 T voxel-based whole-brain white matter maps in 21 patients. This increase of FA was positively associated with treatment response. However, Nickl-Jockschat *et al.* (2016) did not detect any white matter alterations associated with ECT in 20 patients when studying at 3 T with tract-based spatial statistics (TBSS), which focuses on the most compact white matter skeleton. These inconsistent results could be due to small sample sizes, to differences in study populations, and to the major methodological differences between these studies. Furthermore, none considered seizure quality parameters or included patient control groups.

Previous studies have tried to predict ECT response using rating scales, symptom clusters, or clinical characteristics such as depressive episode length and history of medication failure (Hickie *et al.*, 1996; De Vreede *et al.*, 2005; Haq *et al.*, 2015). In neurobiological studies, larger amygdala (ten Doesschate *et al.*, 2014), smaller inferior frontal gyrus gray matter (Oudega *et al.*, 2014), and larger anterior cingulate cortex volume (Redlich *et al.*, 2016) were associated with treatment response. However, no study used DTI to investigate potential predictors for treatment response.

The aims of this study were to investigate influences of ECT on white matter structure. We expect that these influences should differ from regular changes in healthy controls (HC) or treatment effects in patients receiving non-ECT treatment (NON-ECT) – inpatient treatment with medication and psychotherapy. Furthermore, white matter changes post-ECT should be associated with clinical response and seizure quality parameters. Lastly, in line with previous gray matter studies, we expect that baseline white matter coherence is a potential predictor for treatment response.

Methods and materials

Participants and study design

One hundred and seventy subjects – 106 subjects diagnosed with current major depressive disorder and 64 HC – participated in the present study. Thirty-five depressed patients were treated with ECT and 71 received in-patient treatment. Patients were recruited naturalistically with treatment being assigned based on clinical decisions independent from study participation. All subjects were diagnosed with the Structural Clinical Interview for DSM-IV-TR (Wittchen *et al.*, 1997) to confirm the psychiatric diagnosis or the lack thereof. For study inclusion and exclusion criteria, see online Supplementary Methods 1.

Thirteen subjects (10 HC and three ECT) were lost to follow-up. Two participants had to be excluded after clinical assessment, due to high self-reported depressive symptoms in the absence of a major depressive episode (one HC), or a bipolar disorder diagnosis (one NON-ECT). In the process of image quality control (see 'Methods' section below), six additional subjects (one HC, three ECT, one NON-ECT) had to be excluded. Therefore, the final sample comprised 29 ECT, 69 NON-ECT, and 52 HC included in all further analyses.

We conducted a non-randomized prospective study. The three groups (ECT, NON-ECT, HC) were investigated at two time points each (T_0, T_1). In the ECT group, patients were measured before treatment (T_0), and shortly after finishing treatment (T_1). The pre–post interval in control groups was 6–7 weeks adjusted for average ECT series length (Table 1). The average time between the last ECT and the post-MRI scan was 4.21 days (S.D. = 4.15). Brief-pulse ECT was conducted three times a week using an integrated instrument (Thymatron IV; Somatics Inc, Venice, FL, USA; number of sessions: $M = 13.86$, S.D. = 3.53). Energy dosage elevation was considered between ECT sessions if the primarily induced seizure activity lasted <25 s. For more details on ECT procedure and parameters, see online Supplementary Methods 2.

The three groups did not differ in days between scans, sex, and IQ (all $ps > 0.176$; see Table 1). We controlled for age in all subsequent analyses, as the three groups differed significantly ($p < 0.001$). As expected, the two patient groups ECT and NON-ECT had different clinical characteristics and medications. Patients treated with ECT had a more severe course of illness (e.g. more hospitalizations, see Table 1) and more antipsychotic medication (see Table 1) compared with NON-ECT. We used the Medication Load Index (MedIndex; Redlich *et al.*, 2014) – a composite measure of total medication load reflecting dose and number of prescriptions irrespective of active components – and furthermore chlorpromazine equivalent doses (CPZ; Gardner *et al.*, 2010) to measure medication intake. Medication – measured by CPZ and MedIndex – in both groups did not change between scans (all $ps > 0.548$). For more medication details and comorbidities, see online Supplementary Methods 3.

This study was approved by the ethics committee of the Medical Faculty of Muenster University and all subjects gave written informed consent prior to the examination. They received financial compensation for participation after the testing session.

DTI data acquisition

Data were acquired using a 3 T whole body MRI scanner (Gyroscan Intera, Philips Medical Systems, Best, the Netherlands), as reported earlier (Repple *et al.*, 2017). The DTI data were acquired in 36 axial slices, 3.6 mm thick with no gap (acquired matrix 128 × 128), resulting in a voxel size of 1.8 mm × 1.8 mm × 3.6 mm. The echo time was 95 ms and the repetition time was 9473 ms. A *b*-value of 1000 s/mm^2 was used for 20 diffusion-weighted images, with isotropic gradient directions plus one non-diffusion-weighted ($b_0 = 0$) image. In sum, 21 images per slice were used for diffusion-tensor estimation. The total data acquisition time was approximately 8 min per subject. During the experiment, subjects lay supine in the MRI scanner with their head position being stabilized.

Image processing

Preprocessing and analysis were performed with the FSL FMRIB Software Library v10.0 [http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, FMRIB, Oxford Center for Functional MRI of the Brain,

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Table 1. Demographic and clinical characteristics of the sample

Characteristic	ECT[a] ($n = 29$)	NON-ECT[a] ($n = 69$)	HC[a] ($n = 52$)	p (HC *v.* ECT *v.* NON-ECT)	p (ECT *v.* NON-ECT)
Sociodemographic					
Gender	♀19♂10	♀31♂38	♀27♂25	0.176[b]	0.063[b]
Age, years	46.59 ± 8.23	34.94 ± 11.77	40.73 ± 11.98	<0.001[c]	<0.001[d]
Days between scans	45.79 ± 18.70	48.32 ± 9.46	51.21 ± 17.99	0.377[c]	0.377[d]
Verbal IQ_{MWTB}	111.83 ± 16.17	112.88 ± 13.48	115.52 ± 11.43	0.494[c]	0.740[d]
Questionnaires					
HAMD T_0	25.58 ± 6.29	22.81 ± 4.54	0.83 ± 1.34	<0.001[c]	0.016[d]
HAMD T_1	12.97 ± 8.64	12.55 ± 8.14	0.85 ± 1.50	<0.001[c]	0.822[d]
ΔHAMD	12.62 ± 8.91	10.26 ± 8.15	−0.02 ± 1.91	<0.001[c]	0.206[d]
Clinical					
Depression, episodes	6.69 ± 6.90	4.19 ± 5.95	–	–	0.073[d]
Hospitalization, No.	3.62 ± 2.69	1.81 ± 1.43	–	–	0.002[d]
Duration of illness (years)	13.09 ± 11.37	7.93 ± 8.42	–	–	0.033[d]
Medication					
T_0 medication load	3.83 ± 1.67	1.88 ± 1.09	–	–	<0.001[d]
T_1 medication load	3.90 ± 2.09	2.23 ± 1.41	–	–	<0.001[d]
ΔMedication load	−0.07 ± 2.40	−0.35 ± 1.05	–	–	0.552[d]
T_0 CPZ	191.37 ± 166.19	29.49 ± 54.45	–	–	<0.001[d]
T_1 CPZ	170.41 ± 169.49	26.77 ± 49.45	–	–	<0.001[d]
ΔCPZ	20.96 ± 158.75	2.73 ± 47.63	–	–	0.548[d]

[a]Numbers present either absolute numbers or mean plus standard deviation.
[b]χ^2-test (two-tailed).
[c]*F*-test (two-tailed).
[d]*t* test (two-tailed).
Concentration deficits: concentration deficit was rated by clinicians based on clinical presentation on a scale from 0 to 6 points. 0 resembles no difficulties in concentrating, while 6 was rated when participants were unable to read or converse without great initiative (48); CPZ, chlorpromazine equivalent doses; ECT, group treated with electroconvulsive therapy; HAMD, Hamilton Depression Rating Scale; HC, healthy controls; NON-ECT, group treated without ECT.

University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK (Jenkinson *et al.*, 2012)]. For each subject, diffusion-weighted images were corrected for motion and eddy-current distortions using the eddy-correct utility in FSL with b_0 image as reference for alignment. The reference images underwent automated skull stripping before diffusion tensor estimation using the FSL FDT (Bihan, 2003). This yielded an estimation of FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) for each voxel.

To ensure data quality, all raw DTI and FA images were visually inspected. If the estimated mean displacement provided by the eddy-correct log file was larger than three times the standard deviation of all subject's mean displacement, subjects were excluded (see above). Outliers based on FA maps were detected using the homogeneity of covariance test (>2 standard deviations) provided by VBM8-toolbox (http://dbm.neuro.unijena.de/vbm).

Tract-based spatial statistics

TBSS was performed to reduce partial volume effects and registration misalignments (Smith *et al.*, 2006). The FA images were registered to the FMRIB58 FA template and averaged to create a mean FA image. A white matter skeleton was created with an FA threshold of 0.2 and overlaid onto each subject's registered FA image. For each subject, the maximum weighted for distance FA value orthogonal to the skeleton was moved to skeleton space for group-level comparisons. The same registration was performed on MD, RD, and AD values. Factorial models for repeated measures in more than two groups are not yet implemented in FSL (Winkler *et al.*, 2014). Therefore, to investigate changes over time between groups, we calculated difference images subtracting pre- from post-voxel values (Ganzola *et al.*, 2017). To test for statistical significance, we used the non-parametric permutation testing implemented in FSL's randomize (Winkler *et al.*, 2014) with 5000 permutations. Threshold-Free Cluster Enhancement (TFCE) (Smith and Nichols, 2009) was used to correct for multiple comparisons using the default values provided by the --T2 option optimized for TBSS. TFCE is a method for thresholding that allows richer and more interpretable outputs (Smith and Nichols, 2009). TFCE can be seen as a generalization of the cluster mass statistics (Bullmore *et al.*, 1999), and uses spatial neighborhood information in a non-linear image processing to increase sensitivity and boost the height of spatially distributed signals without changing the location of their maxima. Voxel-wise levels of significance, corrected for multiple comparisons, are then calculated with standard permutation testing by building up the null distribution (across permutation of the input data) of the maximum (across voxels) TFCE scores, and then using the 95th percentile of the null distribution to threshold signals at corrected $p < 0.05$. This allows to estimate cluster sizes corrected for the

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family-wise error (FWE; $p < 0.05$, 5000 permutations). MNI coordinates for peak voxel and cluster sizes were derived with FSL Cluster and the corresponding white matter tract retrieved from the ICBM-DTI-81 white matter atlas (Mori *et al.*, 2006; Pekar *et al.*, 2007).

Analysis

Statistical analyses on the demographic data were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA). We assessed treatment efficacy in a repeated-measures analysis of covariance (ANCOVA) in SPSS with the dependent variable sum of Hamilton Depression Scale (HAMD) (Hamilton, 1960), a measure of depressive symptom severity, for each time point, the within-subject factor time (T_0 *v.* T_1), the between-subject factor treatment (ECT *v.* NON-ECT), and the nuisance variables age, sex, and days between scans.

1. Longitudinal changes in diffusion metrics (FA, MD, RD, AD) in the ECT sample were established using paired *t* tests within FSL.
2. For the investigation of a group by time interaction, we performed two analyses: Permutation of repeated measures, three-group ANCOVAs via 'FSL's randomize' is not yet implemented. Therefore, we first extracted a single mean MD value for each subject from the result mask of the paired *t* test (ECT T_1 *v.* ECT T_0). With these extracted values, we performed a proper repeated-measures ANCOVA within SPSS with group (ECT *v.* NON-ECT *v.* HC) as between-subject factor and time (T_0 *v.* T_1) as a within-subject factor. Age, sex, and total intracranial volume (TIV) were included as covariates. Post-hoc *t* tests and ANCOVAs were performed within SPSS to further investigate group differences, especially comparing the two patient groups while controlling for clinical variables (illness severity, measured by number of hospitalization and number of depressive episodes) and medication strategies (measured by MedIndex and CPZ).
   Second, to compare whole-brain changes in diffusion metrics (ΔFA, ΔMD, ΔAD, ΔRD) over time between groups, difference images were analyzed using *t* tests comparing ECT to both control groups, NON-ECT and HC, correcting for age, sex, time between scans, and TIV as recommended by FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM).
3. Next, to test the influence of seizure properties on white matter, difference images (ΔFA, ΔMD, ΔAD, ΔRD) were correlated with mean seizure duration, measured by seizure EEG activity in seconds. Furthermore, for exploratory analyses with additional ECT parameters, we performed correlational analyses with extracted Delta MD values (from the results mask ECT T_1 *v.* T_0) and ECT parameters (online Supplementary Methods 2).
4. To assess the associations between white matter integrity and treatment response in both patient groups, we conducted exploratory correlational analyses. To find associations of treatment response, baseline DTI images and changes in DTI metrics were correlated with changes in HAMD (ΔHAMD = $HAMD_{T0} - HAMD_{T1}$), as a measure of treatment efficacy (Hamilton, 1960). We repeated these analyses within the results mask from the longitudinal results (ECT T_1 *v.* ECT T_0), to check for anatomical overlap of these two analyses.

For all analyses with T_0 images, age, sex, and TIV were included as nuisance variables. For all analyses with difference images (ΔFA, ΔMD, ΔAD, ΔRD),, we used age, sex, TIV and days between scans as nuisance variables.

Results

Longitudinal effects

We investigated depressive symptom severity comparing HAMD values over time (T_0, T_1). We found a significant main effect of time [$F_{(1,92)} = 6.66$, $p = 0.011$], as both treatments reduced depression severity (Table 1). We found neither a main effect of treatment (ECT *v.* NON-ECT) nor a treatment × time interaction (all $p > 0.478$) with both treatments being equally effective for the respective patient cohort.

ECT patients had significantly higher MD at T_1 compared with T_0 in several right-sided white matter tracts including the uncinate fasciculus, the posterior limb of internal capsule, the inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus ($p_{FWE} = 0.018$, $k = 2008$, $x = 31$, $y = 0$, $z = -32$; Figure 1, online Supplementary Results 1). There was a trend of increased AD ($p_{FWE} = 0.056$) and RD ($p_{FWE} = 0.055$), while no effect was detected for FA ($p_{FWE} = 0.93$). No decreases of parameters were observed (all $p_{FWE} > 0.31$).

Repeated-measures ANCOVA

A repeated-measures ANCOVA with the extracted MD values (from the significant cluster in the ECT group time effect analysis; T_0 *v.* T_1) revealed a significant group × time interaction [$F_{(2,147)} = 5.60$; $p = 0.005$]. Post-hoc *t* tests showed that the increase in MD is significant in the ECT group [$MD_{pre} = 0.00072$, $MD_{post} = 0.00074$, $t(28) = 4.67$, $p < 0.001$] and that this increase (ΔMD) is significantly higher in the ECT group compared both with NON-ECT [$t(96) = 3.2$, $p = 0.002$] and to HC [$t(79) = 2.89$, $p = 0.005$]. For a bar graph, see Fig. 2.

Furthermore, when comparing patient groups, ΔMD was significantly higher in the ECT group compared with NON-ECT even after correcting for baseline CPZ scores [$F_{(1,92)} = 17.45$, $p < 0.001$], MedIndex [$F_{(1,92)} = 19.22$, $p < 0.001$], ΔCPZ scores [$F_{(1,92)} = 34.45$, $p < 0.001$], ΔMedIndex scores [$F_{(1,92)} = 33.86$, $p < 0.001$], number of depressive episodes [$F_{(1,92)} = 34.49$, $p < 0.001$], or number of hospitalizations [$F_{(1,92)} = 30.63$, $p < 0.001$] in an ANCOVA already including age, sex, and TIV as covariates.

Whole-brain comparison of ΔDTI images

ΔAD was significantly higher in ECT patients compared with NON-ECT ($p_{FWE} = 0.037$, $k = 1251$, $x = -40$, $y = -3$, $z = 23$) predominantly in the left anterior corona radiata (online Supplementary Results 2). There was no significant difference between ECT and NON-ECT in ΔFA ($p_{FWE} = 0.68$), ΔMD ($p_{FWE} = 0.11$), or ΔRD ($p_{FWE} = 0.16$). ΔAD, ΔMD, ΔRD, ΔFA in ECT did not differ significantly compared with HC (all $p_{FWE} > 0.485$).

Association with ECT parameters

A significant negative correlation with seizure duration in ΔFA was present ($p_{FWE} = 0.039$, $k = 3478$, $x = 7$, $y = 29$, $z = 8$); longer seizure durations were associated with decreases in FA over time mostly in the corpus callosum, the corona radiata, and the internal capsule (see online Supplementary Results 3) in FSL.

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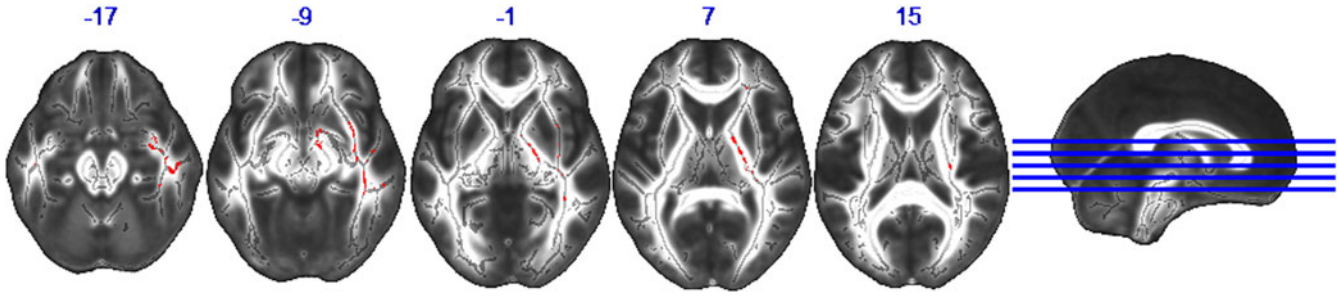


Fig. 1. Longitudinal increase of MD in ECT sample. Axial slices with corresponding *y*-axis values (MNI) are presented. Red areas represent voxels, where a significant increase of mean diffusivity was detected after ECT in the ECT sample ($p_{FWE} < 0.05$). MD, mean diffusivity.

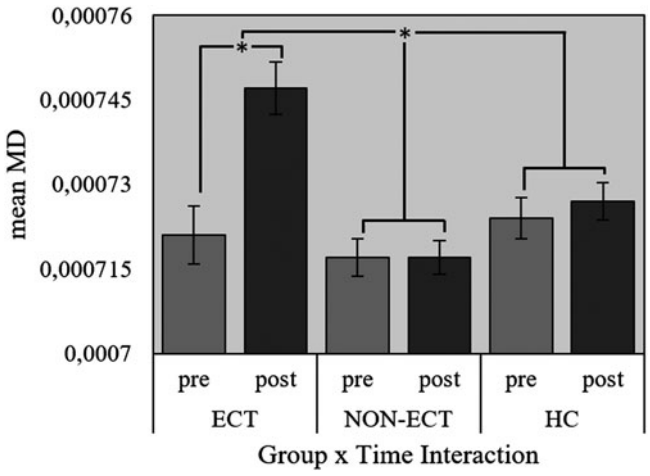


Fig. 2. Longitudinal effects of mean diffusivity in all groups. Bar graph displaying mean MD values (extracted from the results mask of the ECT group pre- *v.* post-analysis) for both time points [pre (T_0) = before first ECT treatment, post (T_1) = after last ECT treatment]. MD, mean diffusivity; ECT, group treated with electroconvulsive therapy; NON-ECT, group treated without ECT; HC, healthy controls. *Significant post-hoc increase in MD in ECT group [$MD_{pre} = 0.00072$, $MD_{post} = 0.00074$, $t(28) = 4.67$, $p < 0.001$].

MD, RD, AD were not significantly associated with seizure duration (all $p_{FWE} > 0.11$).

In further exploratory analyses within the ECT sample, we did not find any correlation of ΔMD with other ECT parameters such as the average electrical charge ($p = 0.50$), maximum electrical charge ($p = 0.21$), the difference score (charge last ECT – charge first ECT; $p = 0.50$), total number of ECT treatments ($p = 0.93$), days between last ECT and T_1-MRI scan ($p = 0.36$), and total seizure duration (across all ECT treatments, $p = 0.12$) in SPSS.

Association of therapy response

We found a significant positive correlation of ΔHAMD with FA ($p_{FWE} = 0.044$, $k = 4404$, $x = 36$, $y = -38$, $z = 12$) and negative correlations with MD ($p_{FWE} = 0.045$, $k = 6107$, $x = 36$, $y = -38$, $z = 12$) and RD ($p_{FWE} = 0.047$, $k = 2541$, $x = 33$, $y = -35$, $z = 13$) at T_0 in the ECT subsample. Thus, higher FA and lower MD and RD values at baseline were positively associated with higher treatment response. The effect was mostly present in posterior fiber tracts including the splenium of corpus callosum, internal capsule, and corona radiata (Fig. 3, online Supplementary Results 4). No association was present for AD (all $p > 0.152$). For an additional analysis of baseline DTI measures with therapy response within the results mask of the ECT T_1 *v.* T_0 analyses, we again could show a positive FA and negative RD and MD correlation with ΔHAMD, for more information please see online Supplementary Material 5.

We did not observe an association of baseline DTI markers with treatment response in the NON-ECT group (all $p_{FWE} > 0.13$). Furthermore, we did not observe an association of ΔDTI metrics with ΔHAMD in the ECT (all $p_{FWE} > 0.30$) or NON-ECT group (all $p_{FWE} > 0.22$).

Neither age, sex, time since first symptoms, time in weeks of current depressive episode, number of depressive episodes, number of hospitalizations, total education years, Medication Index at T_0 nor CPZ score at T_0 (all $p > 0.36$) were associated with ΔHAMD in the ECT subsample.

Discussion

Longitudinal changes

Within-group analyses revealed a widespread right-sided increase of MD in the ECT group after treatment compared with baseline. As most patients were stimulated unilaterally on the right side, this could underlie the laterality of the MD increase. This finding is in line with several ECT-induced gray matter changes, which are most frequently reported in the right hemisphere (Yrondi *et al.*, 2017). Further, the MD increase in the ECT group was significantly greater compared with the NON-ECT group. Even more, the MD increase in the ECT group was significantly higher compared with the NON-ECT patient group when correcting for all indices of disease severity and medication, supporting the idea of ECT treatment-specific white matter alterations. The specificity of these findings is further supported by ECT parameter correlations: mean seizure duration was associated with FA decrease over time in several major longitudinal and association fibers pointing toward a negative effect of longer seizure activity on white matter integrity. On the other hand, the longitudinal changes in fiber structure were not associated with therapy response. While the increase in MD seems to be specific for ECT, it does not seem to be involved in its antidepressant effect. This is in line with the results in gray matter showing repeatedly that changes in volume post-ECT are not associated with psychopathology (Redlich *et al.*, 2016; Oltedal *et al.*, 2018; Sartorius *et al.*, 2019).

A possible although speculative explanation for the MD increase could be a mild ECT-induced increase in water concentration due to an increased permeability of the blood–brain barrier. Preclinical and clinical evidence show that ECT may result in a small, transient breach in the blood–brain barrier [for review see Andrade and Bolwig (2014)]. These white matter fiber

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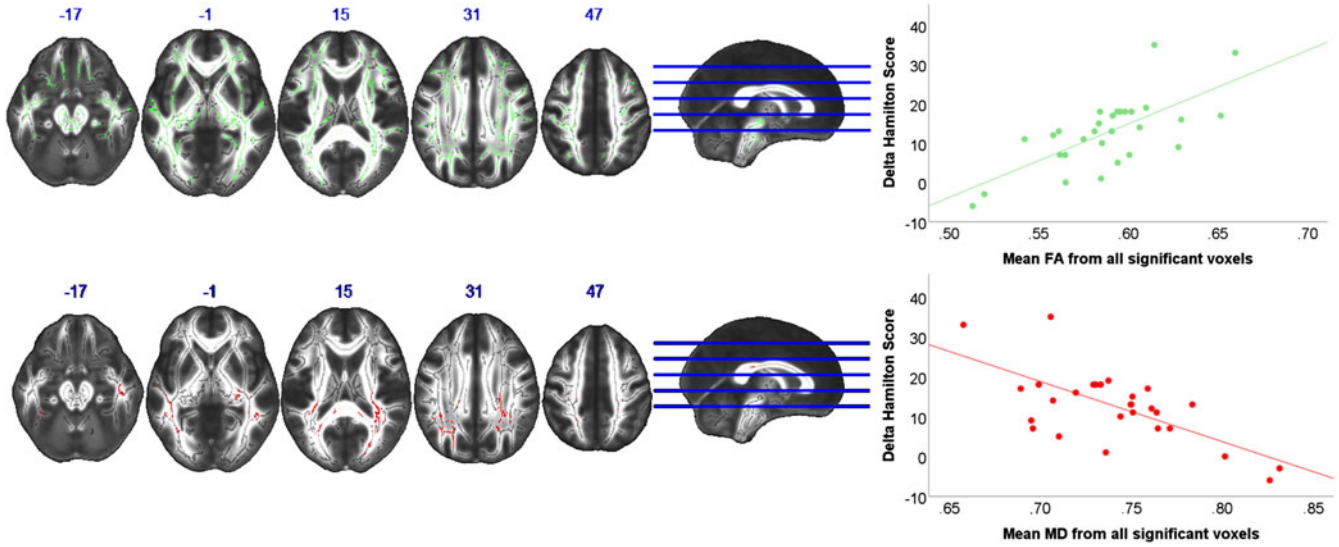


Fig. 3. Correlation of baseline (*a*) FA and (*b*) MD maps with clinical response. Top: Positive correlation FA; bottom: negative correlation MD. On the left axial slices with corresponding *y*-axis values (MNI) are presented. Green (FA)/red (MD) areas represent voxels, where a significant association between baseline FA/MD and ΔHAMD was found ($p_{FWE} < 0.05$). Scatterplot on the right shows the association of ΔHAMD and extracted mean baseline FA/MD values from all significant voxels of corresponding TBSS analyses. FA, fractional anisotropy; MD, mean diffusivity; HAMD, sum score of the Hamilton depression scale; ΔHAMD, Difference Score ($HAMD_{T0} - HAMD_{T1}$), high positive score reflects a good clinical response.

impairments may be of clinical relevance in ECT, but future studies with additional neuropsychological testing and repeated measures during follow-up are needed to shed more light on the meaning and persistence of these alterations.

These results are in contrast to the study of Lyden *et al.* (2014), who could demonstrate ECT-induced increases of FA that were associated with treatment response. However, their patient sample was younger, was tapered off of psychiatric medication, stimulus dosing was established using the titration method, and no increase of stimulation dose in the course of the ECT series was reported. Therefore, it is very likely that our sample received higher energy doses, which are known to lead to a higher antidepressive response (UK ECT Review Group, 2003), but also higher temporary cognitive impairments (Semkovska and McLoughlin, 2010; Tor *et al.*, 2015).

Correlates of therapy response

Coherent fiber structure at baseline – higher FA and lower MD and RD – was positively associated with therapeutic effect (higher decrease in Hamilton Depression score) within the ECT group. It is hypothesized that the brain's ability to suppress a generalized seizure is therapeutic rather than the seizure itself (Folkerts, 1996; Sackeim, 1999; Kranaster *et al.*, 2013). Therefore, brain signaling necessary to successfully inhibit increased seizure activity might rely on intact white matter integrity. Alternatively, coherent fiber structure could be a prerequisite for a generalized seizure and its antidepressant effect. Future studies need to investigate how white matter integrity serves as a prerequisite for ECT treatment success. No other clinical or sociodemographic variables at T_0 were associated with therapy response highlighting the necessity to explore neurobiological markers for ECT response.

Limitations

We did not perform cognitive screening pre- or post-ECT treatment, restricting the interpretability of our results. Therefore, future studies need to investigate cognitive impairments with standard neuropsychological testing to further elucidate our findings.

Furthermore, the use of exploratory correlational analyses is a limitation of this study. Interpretations need to be treated with caution, as they are not corrected for multiple testing. However, they offer helpful preliminary insights into further research regarding the relationship of ECT quality parameters and white matter integrity.

The ECT and NON-ECT group differed significantly in clinical characteristics such as age, medication intake, and chronicity. The recruitment of patients in a naturalistic setting, involving different indications for drug or ECT treatment, leads to different sample characteristics, which is a clear limitation of this study. However, when correcting for age, antipsychotic medication, and illness severity, the ΔMD increase in the ECT group after treatment was still significantly higher, which points toward an ECT-specific effect on MD.

We could not detect an association of white matter changes and therapy response. While the antidepressant effect might be caused by neurotrophic mechanisms on white matter induced by ECT, it could be possible that these changes might be too subtle to be detected by our DTI scans, and moreover, they might have been overshadowed by a mild ECT-induced water increase in ΔMD. Therefore, measuring patients solely directly following treatment might constitute a limiting factor. Future studies should recruit patients repeatedly at different times after treatment (e.g. during, directly after, 2 weeks after, 6 months after) to further disentangle short-term from long-term changes.

Lastly, while our sample size is the largest reported, it is still small, which might be the reason for the absence of group differences over time between ECT and HC in the whole-brain analysis. Nonetheless, to the best of our knowledge, this longitudinal ECT DTI study is the one with the largest sample size so far, the first study to have a large depressed control group, and the first that investigated ECT parameters.

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Conclusion

We could show that ECT is associated with white matter alterations. Additionally, baseline FA, MD, and RD values in a large cluster were significantly associated with therapy response in the ECT sample, which could support the future quest for a clinically suitable biomarker for therapy response prediction of ECT.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719000758

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Conflict of interest. V. Arolt is a member of the advisory board of, or has given presentations on behalf of, the following companies: Astra-Zeneca, Janssen-Organon, Lilly, Lundbeck, Servier, Pfizer, Otsuka, and Trommsdorff. These affiliations are of no relevance to the work described in the manuscript. H. Kugel has received consultation fees from MR:comp GmbH, Testing Services for MR Safety. This cooperation has no relevance to the work that is covered in the manuscript. The other authors declare no conflict of interest. All authors have approved the final article.

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