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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods 1. Questionnaire Measures and Medication Load

The Hamilton Rating Scale of Depression (HDRS)\(^1\) was conducted by a clinical interviewer at both time points as an objective measure to assess the severity of depressive symptoms. Additionally, the Beck Depression Inventory\(^2\) was used as self-evaluation-questionnaire. For measuring total medication load in MDD patients we used a strategy described earlier\(^3\). Each medication was coded as absent = 0, low = 1 (equal or lower average dose), or high = 2 (greater than average dose) with reference to the midpoint of the Physician’s Desk Reference recommended daily dose range. We calculated a composite measure of total medication load for each individual, reflecting dose and variety of different medications taken, by summing all individual medication.

eMethods 2. Electroconvulsive Therapy

All patients received unilateral ECT. In three patients, treatment was switched to bilateral ECT because of insufficient response to unilateral treatment. Physiological monitoring included two-lead electroencephalogram (EEG), single-lead electromyography (EMG), ECG, and blood pressure monitoring. The initial stimulus intensity was determined using the age method. Re-stimulation, including dosage elevation in steps of 5–10%, was considered during single ECT sessions if the primarily induced seizure activity lasted less than 25 seconds in EEG. Due to increased seizure threshold throughout the course of ECT, stimulus intensity was adapted in the same manner. The mean stimulus intensity was 51.95% (SD=18.80), the mean stimulus duration 6.98 seconds (SD=0.50), and the mean pulse frequency 40.17Hz (SD=10.16). The measured mean seizure durations were 42.86 seconds (EEG; SD=10.08) and 23.98 seconds (EMG; SD=10.64). The mean postictal suppression index was 93.86 % (SD=2.77) while the seizure generalization index was 73.27 % (SD=8.59). Also, MRI, electrocardiography (EKG), and laboratory blood tests were carried out to exclude severe somatic pathology (ASA physical status>3). All patients were anesthetized with methohexital sodium or propofol, and a muscle relaxant (succinylcholine) was administered.

eMethods 3. Data Collection and Voxel-Based Morphometry

T1-weighted high resolution anatomical images were acquired before (\(M = 6.69\) days; \(SD = 6.14\)) and after (\(M = 4.58\) days, \(SD = 4.90\)) the ECT series (Gyroscan Intera 3T, Philips Medical Systems, Best, NL) with a 3D fast gradient echo sequence (‘Turbo Field Echo’, TFE), TR=7.4 ms, TE=3.4 ms, FA=9°, 2 signal averages, inversion prepulse every 814.5ms, acquired over a field of view of 256(FH)x204(AP)x160(RL) mm, phase encoding in AP and RL direction, reconstructed to cubic voxels of 0.5x0.5x0.5 mm.

The VBM8-toolbox (http://dbm.neuro.unijena.de/vbm) was used for preprocessing the structural images with default parameters as described in our previous work\(^4\). Briefly, images were bias-corrected, tissue classified, and normalized to MNI-space using linear (12-parameter affine) and non-linear transformations, within a unified model including high-dimensional DARTEL-normalization. Gray matter segments were modulated only by non-linear components in order to preserve actual GM values locally (modulated GM volumes). The modulated gray matter images were smoothed with a Gaussian kernel of 8 mm FWHW.

eMethods 4. Pattern Classification in Medicine-Only Sample

In order to examine the ability to classify the MED (non-ECT) sample, the MED sample was split into responders (n=9) and non-responders (n=14; criterion was <50% individual symptom relief according to HDRS scores). As for classification of ECT response, the ability of the SVM and GPC to predict therapy response using pre-treatment gray matter data was evaluated using a leave-one-subject-out cross-validation. A conservative analysis strategy was employed, using the preprocessed and smoothed modulated whole-brain GM data without any embedded feature selection methods. The prediction of response to medication by structural images obtained before yielded no accuracy rates significantly above chance level (accuracy rates < 50%). In line with the regression of ECT response, a support vector regression (SVR) was additionally conducted for the MED sample, as described in the method section. The SVR was not able to significantly predict continuous symptom relief according to HDRS using the MED sample (n=23, \(r=0.09, P=0.681\)). This performance was significantly poorer than the ECT response prediction (Fisher’s \(z = 2.278, P=.011\)).

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eMethods 5. Supplementary Univariate Methods

To determine the association between gray matter changes across time (T2–T1) and clinical response represented by individuals’ HDRS percent score changes in patients treated with ECT, the gray matter values of the resulting peak voxel of this ECT-T2>ECT-T1 analysis were extracted for both time points and further analyzed by using SPSS Statistics 21. Additionally, the total intracranial volumes were extracted and investigated. The individual gray matter changes were then correlated with the percentage of symptom relief represented by the HDRS scores changes (1-HDRS T2/HDRS T1).

To detect potential associations between symptom improvement and demographic (age, sex) as well as clinical characteristics (number of episodes, duration of illness, time since first in- and outpatient treatment, lifetime duration of inpatient treatment and duration of index episode) we conducted correlation analyses for both the ECT sample as well as the MED sample.
eResults 1. Cross-sectional Effects of Group at Time 1

In line with previous studies and in both patient groups, reduced GMVs at T1 were found in neural regions previously reported as showing abnormalities in individuals with unipolar depression. Compared to HC, abnormalities included reduced GMVs in the anterior cingulate gyrus (ECT: x=-9, y=32, z=3, Z=4.47, k=403, P<0.00001; MED: x=-9, y=28, z=-5, Z=4.63, k=438, P<0.00001), precuneus (ECT: x=-12, y=-58, z=48, Z=4.70, k=559, P<0.00001; MED: x=15, y=-49, z=48, Z=4.54, k=496, P<0.00001), fusiform gyrus extending to the hippocampus (ECT: x=-21, y=-84, z=-11, Z=4.69, k=552, P<0.00001; MED: x=-33, y=30, z=-27, Z=4.17, k=424, P=0.00002), lingual gyrus and cerebellum, superior temporal gyrus (ECT: x=-60, y=-12, z=2, Z=4.05, k=448, P=.00003), and middle temporal gyrus respectively (MED: x=-52, y=-25, z=0, Z=3.93, k=970, P=.00005). The ECT sample additionally showed GMV reductions within the caudate nucleus compared to HC (x=24, y=16, z=12, Z=3.50, k=467, P=.00025) and reductions within the putamen compared to the MED sample (x=16, y=10, z=-2, Z=3.69, k=412, P=.0001).

eResults 2. Longitudinal Effects of Treatment on Gray Matter Volumes

Post-hoc analysis: The post hoc analysis of the effects of ECT on GMVs yielded significant increases in the hippocampal gray matter, extending to insula, amygdala, putamen, fusiform gyrus, superior temporal gyrus, and temporal pole (Left: x=-28, y=-9, z=18, Z=7.81, k=10133, P<0.00001). Additionally, volume increases were found in thalamic and caudate nucleus areas (x=-10, y=-28, z=18, Z=5.43, k=1291, P<0.00001) as well as in the supplementary motor area and the middle cingulate gyrus (x=3, y=-1, z=43, Z=4.42, k=1721, P<0.00001), and also the right hippocampus extending to the amygdala (x=38, y=-9, z=-20, Z=4.34, k=1378, P<0.00001).

The post-hoc analyses of cross sectional effects at T2 revealed, that whole brain GMV reductions in the ECT sample, as present at T1, were entirely normalized after ECT treatment, compared to HC. Moreover, the ECT sample even showed a slightly increased hippocampal (x=-33, y=-7, z=-24, Z=4.51, k=404, P=.00003) and prefrontal (x=-15, y=42, z=-8, Z=4.90, k=567, P<0.00001) GMV at T2 compared to HC. The analysis of the effects of medication in the MED sample yielded no significant volume changes during treatment.

Associations between volume increases and clinical response: The correlation analyses between GMV changes within the ECT group and symptomatic improvements yielded no significant associations, neither for the hippocampal cluster, nor for the thalamic, striatal, temporal areas and total intracranial volume (all Ps>0.07). Even when controlling for age, sex, and clinical parameters, no significant associations were found.

eReferences
eFigure. Discriminative Maps for SVM Classifier

Discriminative map for SVM classifier for the trained pattern of ECT response. The figure is depicting the most contributing feature weights (MNI = 12x) showing the subgenual cingulate gyrus. Abbreviations: ECT, Electro convulsive therapy; MNI, Montreal Neurological Institute.
**eTable. Lifetime Comorbidities**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>ECT Sample (n = 23)</th>
<th>MED Sample (n = 23)</th>
<th>X²</th>
<th>P Value</th>
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*Abbreviations:* ECT—Electroconvulsive Therapy; MED—Medication.