**Supplementary Methods 1:**

**Study inclusion and exclusion criteria**

We recruited Caucasian subjects varying in age from 18-59 years. Patients that were treated predominantly for depressive symptoms were recruited from local psychiatric hospitals. Exclusion criteria comprised any neurological abnormalities, history of seizures, head trauma or unconsciousness, not adequately substituted hypothyroidism, severe physical impairment (e.g. cancer, instable diabetes, epilepsy etc.), pregnancy, claustrophobia, color blindness and general magnetic resonance imaging contradictions (e.g. metallic objects in the body). Further, patients with comorbid life-time diagnoses of schizophrenia, schizoaffective disorder or substance dependence were excluded.

**Calculation of medication indices**

The Medication Load Index (MedIndex (Redlich *et al.* 2014)) was calculated as follows: We defined each psychopharmacological medication as absent (= 0), equal to no medication intake, low (= 1), meaning a dosage equal or lower than average, or high (= 2), with a dosage greater than average relative to the midpoint of the daily dose range recommended by Physician’s-Desk-Reference. We calculated the sum of all medication scores, if patients had more than one prescription. Further, chlorpromazine equivalent doses were calculated for antipsychotic medication load based on Gardner et al. (Gardner *et al.* 2010).

**Supplementary Methods 2:**

**Description of electroconvulsive therapy**

All patients started their treatment with right-sided unilateral ECT. In three patients, treatment was converted to bilateral ECT because of insufficient clinical response to unilateral treatment. ECT monitoring included electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (ECG), and blood pressure monitoring. The initial stimulus intensity was calculated using the age method. Re-stimulation, including dosage elevation in steps of 10%, was considered during single ECT sessions if the primarily induced seizure activity lasted less than 25 seconds in EEG. Due to an increasing seizure threshold throughout the course of ECT, stimulus intensity was increased in the same manner. All patients were anesthetized with methohexital sodium or propofol, and a muscle relaxant (succinylcholine) was administered.

**Table Supplementary Methods 2: Overview of ECT parameters.** Mean values and standard deviation of ECT stimulus and quality parameters.

|  |  |  |  |
| --- | --- | --- | --- |
| *Overview of ECT parameters* | | | |
| Parameters | *N* | Mean | SD |
| Number of ECT treatments | 29 | 13.86 | 3.53 |
| Average Seizure Time (EEG) | 29 | 41.62 | 11.18 |
| Average Seizure Time (EMG) | 28 | 22.78 | 10.33 |
| Postictal Suppression Index | 28 | 58.50 | 8.10 |
| Maximum Coherence | 28 | 90.87 | 5.27 |
| Average Stimulus Charge | 28 | 54.05 | 21.53 |
| Maximum Stimulus Charge | 28 | 80.00 | 39.10 |
| Delta Stimulus Charge | 29 | 46.21 | 42.80 |
| *Note:*  n = number of included ECT Patients, *SD* = standard deviation, EEG = electroencephalogram, EMG = electromyography | | | |

Average Seizure Time was measured by EEG in time wave-seizure activity in seconds. Average Muscle Seizure Time was measured by EMG. During ECT treatment, blood circulation of the left arm was cut off temporarily using a blood pressure cuff before Succinylcholin administration to observe muscle seizure activity. Postictal Suppression Index measures successful inhibition of seizure activity calculated by the ratio of EEG amplitude before and after the seizure ceases. Maximum Coherence is a measure of synchrony of seizure activity in both hemispheres. Maximum Stimulus Charge is reported as percentage value of 504 mC (millicoulomb). ΔStimulus Charge is calculated by subtracting the applied charge during the first ECT from the applied charge during last ECT and is therefore a measure of how much applied charge had to be adjusted, an indicator of poor therapeutic outcome. Indeces were calculated automatically by the ECT instrument (Thymatron system IV; Somatics Inc).

**Supplementary Methods 3: Medication and comorbid disorder details in patient groups.**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | ECT1 (*n* = 29) | NON-ECT1 (*n* = 69) | *p* (ECT vs. NON-ECT) |
| T0 |  |  |  |
| Medication load | 3.83 ± 1.67 | 1.88 ± 1.09 | < .0013 |
| CPZ | 191.37 ± 166.19 | 29.49 ± 54.45 | < .0013 |
| Antidepressants | 24 | 63 | .2212 |
| SSNRI | 14 | 31 | .7612 |
| SSRI | 3 | 20 | .0472 |
| NDRI | 2 | 1 | .1532 |
| NaSSA | 8 | 9 | .0832 |
| Tricyclics | 4 | 2 | .0402 |
| Other | 5 | 11 | .8742 |
| Mood stabilizer | 4 | 2 | .0402 |
| Antipsychotics | 20 | 23 | .0012 |
| T1 |  |  |  |
| Medication load | 3.90 ± 2.09 | 2.23 ± 1.41 | < .0013 |
| CPZ | 170.41 ± 169.49 | 26.77 ± 49.45 | < .0013 |
| Antidepressants | 25 | 62 | .6022 |
| SSNRI | 19 | 37 | .2772 |
| SSRI | 2 | 15 | .0772 |
| NDRI | 2 | 4 | .8362 |
| NaSSA | 10 | 11 | .0412 |
| Tricyclics | 3 | 2 | .1262 |
| Other | 3 | 11 | .4702 |
| Mood stabilizer | 5 | 5 | .1632 |
| Antipsychotics | 10 | 23 | .9122 |
| T0-T1 |  |  |  |
| ΔMedication load | -0.07 ± 2.40 | -0.35 ± 1.05 | .5523 |
| ΔCPZ | 20.96 ± 158.75 | 2.73 ± 47.63 | .5483 |
| Depression subtype |  |  |  |
| Psychotic depression | 2 | 0 | - |
| Co-morbid disorders |  |  |  |
| Anxiety disorder | 15 | 41 | .4822 |
| GAD | 0 | 6 | - |
| Panic/Agoraphobia | 5 | 13 | .5822 |
| Specific phobia | 4 | 4 | .1872 |
| PTSD | 3 | 4 | .4252 |
| OCD | 1 | 3 | .8372 |
| Social phobia | 2 | 11 | .2282 |
| Dysthymia | 0 | 5 | - |
| Somatic disorder | 0 | 1 | - |
| Eating disorder | 1 | 5 | .4742 |
| Substance abuse | 1 | 1 | .5232 |
| Personality disorder | 1 | 0 | - |
| Note: 1Numbers represent either absolute numbers or mean plus standard deviation.2 *χ*2-test (two-tailed), 3 *t*-test (two-tailed), \*p < .05, \*\*p < .01, \*\*\*p < .001; Abbreviations: CPZ = chlorpromazine equivalent doses; ECT = group treated with electro-convulsive therapy, GAD = Generalized Anxiety Disorder; NON-ECT = group treatment without ECT; NDRI = norepinephrine-dopamine reuptake inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant, Panic/Agoraphobia = Panic disorder and/or Agoraphobia; PTSD = Posttraumatic stress disorder; OCD = Obsessive compulsive disorder. SSNRI = selective serotine-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor. | | | |

**Supplementary Results 1:**

**Longitudinal Changes of MD in ECT sample**

**T1 > T0**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-*p* | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 2008 | 0.982 | 31 | 0 | -32 |
| 20 | 0.953 | -48 | -19 | -19 |
| 16 | 0.952 | 25 | 33 | 8 |
| 9 | 0.951 | 35 | -3 | -29 |
| 8 | 0.95 | 44 | -7 | -19 |

Probabilities of affected tracts in percent:

|  |  |  |
| --- | --- | --- |
| Region | Laterality | Probability |
| Unclassified | - | 52.63 |
| Cerebral peduncle | R | 1.44 |
| Anterior limb of internal capsule | R | 0.67 |
| Posterior limb of internal capsule | R | 15.61 |
| Retrolenticular part of internal capsule | R | 2.75 |
| Anterior corona radiata | R | 0.77 |
| Posterior thalamic radiation | R | 0.39 |
| Sagittal stratum | R | 10.94 |
| External capsule | R | 12.43 |
| Fornix (cres) / Stria terminalis | R | 0.29 |
| Uncinate fasciculus | R | 2.07 |

**T0 > T1**

No significant results.

On the top dimensions of clusters (number of voxels) and localization of signal peaks (MNI coordinates) are given for regions showing maximal differences of tract-based spatial statistics values (signal peak). Below are the white matter tracts in the cluster based on the JHU ICBM-DTI-81 White-Matter Labels (as implemented in FSL).

Probabilities of affected tracts: It gives the (average) probability of all significant voxels being a member of the different labelled regions within the atlas (JHU ICBM-DTI-81 White-Matter), calculated with the FSL tool “atlasquery”.

**Supplementary Results 2:**

**Differences in Changes over time in AD, *t*-tests. Cluster, MNI coordinates, peak voxel and anatomical specifications.**

**ECT > NON-ECT**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-*p* | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 1207 | 0.963 | -40 | -3 | 23 |
| 17 | 0.95 | -30 | 25 | 30 |
| 14 | 0.95 | -32 | -60 | 21 |
| 13 | 0.951 | -31 | -52 | 25 |

Probabilities of affected tracts in percent:

|  |  |  |
| --- | --- | --- |
| Region | Laterality | Probability |
| Unclassified | - | 95.06 |
| Anterior corona radiata | L | 3.98 |
| Superior corona radiata | L | 0.08 |
| Superior longitudinal fasciculus | L | 0.88 |

**NON-ECT > ECT**

No significant results.

**ECT > HC**

No significant results.

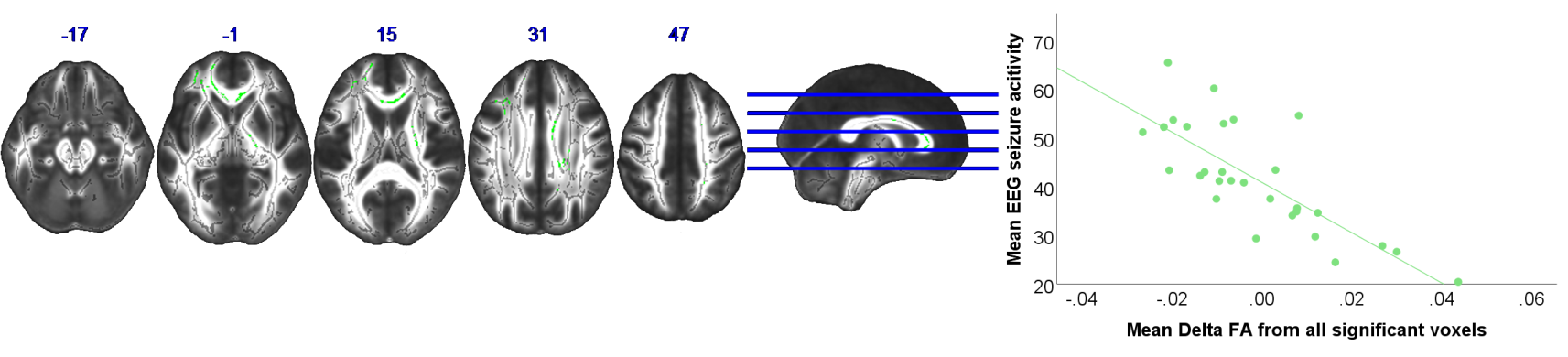
**HC > ECT**

No significant results.

On the top dimensions of clusters (number of voxels) and localization of signal peaks (MNI coordinates) are given for regions showing maximal differences of tract-based spatial statistics values (signal peak). Below are the white matter tracts in the cluster based on the JHU ICBM-DTI-81 White-Matter Labels (as implemented in FSL).

Probabilities of affected tracts: It gives the (average) probability of all significant voxels being a member of the different labelled regions within the atlas (JHU ICBM-DTI-81 White-Matter), calculated with the FSL tool “atlasquery”.

**Figure Supplementary Results 3. Correlational analysis of** Δ**FA with mean seizure activity in seconds**



On the left axial slices with corresponding y-axis values (MNI) are presented. Green areas represent voxels, where a significant negative correlation between Delta FA and seizure activity was found (pFWE< .05). Scatterplot on the right shows the association of seizure activity in seconds (measured with EEG) and extracted mean FA values from all significant voxels of corresponding TBSS analyses.

**Table Supplementary Results 3. Negative association of** Δ**FA with mean length of seizure activity.** Cluster, MNI coordinates, peak voxel and anatomical specifications.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 994 | 0.977 | 7 | 29 | 8 |
| 817 | 0.976 | -31 | 46 | 2 |
| 384 | 0.958 | 25 | -6 | 19 |
| 334 | 0.967 | 25 | -32 | 29 |
| 218 | 0.964 | -15 | 49 | 24 |
| 186 | 0.958 | 11 | -9 | 30 |
| 178 | 0.955 | 18 | -35 | 35 |
| 92 | 0.954 | 15 | -7 | 34 |
| 71 | 0.954 | 23 | -30 | 44 |
| 43 | 0.952 | 16 | -54 | 31 |
| 24 | 0.95 | -21 | 34 | 10 |
| 21 | 0.95 | 29 | -19 | 54 |
| 21 | 0.95 | 3 | -1 | 25 |
| 20 | 0.952 | 26 | -22 | 28 |
| 16 | 0.95 | 12 | 5 | 3 |
| 10 | 0.95 | 27 | -15 | 23 |
| 8 | 0.95 | 31 | -18 | 36 |
| 8 | 0.952 | 12 | -32 | 26 |
| 6 | 0.95 | 21 | -49 | 46 |

Probabilities of affected tracts in percent:

|  |  |  |
| --- | --- | --- |
| Region | Laterality | Probabilty |
| Unclassified | - | 44.91 |
| Genu of corpus callosum | - | 18.00 |
| Body of corpus callosum | - | 8.02 |
| Splenium of corpus callosum | - | 2.33 |
| Cerebral peduncle | R | 0.55 |
| Anterior limb of internal capsule | R | 1.38 |
| Posterior limb of internal capsule | R | 7.48 |
| Retrolenticular part of internal capsule | R | 0.17 |
| Anterior corona radiata | L/R | 0.06/6.18 |
| Superior corona radiata | R | 4.91 |
| Posterior corona radiata | R | 5.32 |
| External capsule | R | 0.12 |
| Superior longitudinal fasciculus | R | 0.58 |

FA: fractional anisotropy; MNI: Montreal Neurological Institute; R: right; L: left.

ΔFA: Difference Images (FAT1‑ FAT0), high positive score reflects increased FA after ECT.

Mean Length of seizure activity: mean length of seizure activity measured by EEG (electroencephalography) during ECT treatment in seconds.

On the top dimensions of clusters (number of voxels) and localization of signal peaks (MNI coordinates) are given for regions showing maximal differences of tract-based spatial statistics values (signal peak). Below are the white matter tracts in the cluster based on the JHU ICBM-DTI-81 White-Matter Labels (as implemented in FSL).

Probabilities of affected tracts: It gives the (average) probability of all significant voxels being a member of the different labelled regions within the atlas (JHU ICBM-DTI-81 White-Matter), calculated with the FSL tool “atlasquery”.

**Supplementary Results 4:**

**Association of T0 A) FA and B) MD C) RD maps with clinical response (ΔHAMD). Cluster, MNI coordinates, peak voxel and anatomical specifications.**

1. Positive association of FA and ΔHAMD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 1290 | 0.976 | 36 | -38 | 12 |
| 650 | 0.955 | -17 | -20 | -9 |
| 615 | 0.957 | -24 | 23 | 11 |
| 476 | 0.956 | -34 | -38 | 9 |
| 457 | 0.959 | -40 | -44 | -4 |
| 288 | 0.956 | -27 | -4 | 25 |
| 250 | 0.952 | -29 | -62 | 0 |
| 146 | 0.952 | 19 | -13 | -7 |
| 95 | 0.951 | 25 | -16 | 7 |
| 47 | 0.951 | 31 | -20 | -8 |
| 47 | 0.95 | -28 | -50 | 30 |
| 46 | 0.952 | 27 | -27 | -4 |
| 44 | 0.951 | -25 | -73 | 17 |

Probabilities of affected tracts in percent:

|  |  |  |
| --- | --- | --- |
| Region | Laterality | Probability |
| Unclassified | - | 19.53 |
| Splenium of corpus callosum | - | 0.07 |
| Cerebral peduncle | R/L | 0.78/5.62 |
| Anterior limb of internal capsule | R/L | 0.09/3.32 |
| Posterior limb of internal capsule | R/L | 3.92/4.95 |
| Retrolenticular part of internal capsule | R/L | 3.92/4.95 |
| Anterior corona radiata | L | 8.96 |
| Superior corona radiata | R/L | 0.85/5.76 |
| Posterior corona radiata | R/L | 5.91/1.88 |
| Posterior thalamic radiation | R/L | 9.32/6.07 |
| Sagittal stratum | R/L | 1.01/2.71 |
| External capsule | R/L | 0.92/1.95 |
| Fornix (cres) / Stria terminalis | R/L | 0.69/0.09 |
| Tapetum | R | 0.09 |

1. Negative association of MD and ΔHAMD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 5527 | 0.965 | 36 | -38 | 12 |
| 580 | 0.955 | 47 | -17 | -20 |

Probabilities of affected tracts in percent:

|  |  |  |
| --- | --- | --- |
| Region | Laterality | Probability |
| Unclassified | - | 49.74 |
| Body of corpus callosum | - | 2.14 |
| Splenium of corpus callosum | - | 8.49 |
| Posterior limb of internal capsule | R/L | 0.60/0.02 |
| Retrolenticular part of internal capsule | R/L | 4.42/1.99 |
| Superior corona radiata | R/L | 1.58/0.29 |
| Posterior corona radiata | R/L | 6.77/3.12 |
| Posterior thalamic radiation | R/L | 6.12/4.57 |
| Sagittal stratum | R/L | 3.85/0.95 |
| Fornix (cres) / Stria terminalis | R | 0.15 |
| Superior longitudinal fasciculus | R/L | 3.04/1.91 |
| Tapetum | R/L | 0.21/0.03 |

1. Negative association of RD and ΔHAMD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 2541 | 0.968 | 33 | -35 | 13 |

Probabilities of affected tracts in percent:

|  |  |  |
| --- | --- | --- |
| Region | Laterality | Probability |
| Unclassified | - | 34.86 |
| Splenium of corpus callosum | - | 7.14 |
| Posterior limb of internal capsule | R | 1.80 |
| Retrolenticular part of internal capsule | R | 13.29 |
| Superior corona radiata | R | 4.00 |
| Posterior corona radiata | R | 16.82 |
| Posterior thalamic radiation | R | 18.47 |
| Sagittal stratum | R | 2.08 |
| External capsule | R | 0.27 |
| Superior longitudinal fasciculus | R | 0.86 |
| Tapetum | R | 0.39 |

MNI: Montreal Neurological Institute; R: right; L: left; FA = fractional anisotropy; MD = mean diffusivity; RD= radial diffusivity; HAMD = sum score of the Hamilton depression scale; ΔHAMD = Difference Score (HAMDT0 – HAMDT1), high positive score reflects a good clinical response

On the top dimensions of clusters (number of voxels) and localization of signal peaks (MNI coordinates) are given for regions showing maximal differences of tract-based spatial statistics values (signal peak). Below are the white matter tracts in the cluster based on the JHU ICBM-DTI-81 White-Matter Labels (as implemented in FSL).

Probabilities of affected tracts: It gives the (average) probability of all significant voxels being a member of the different labelled regions within the atlas (JHU ICBM-DTI-81 White-Matter), calculated with the FSL tool “atlasquery”.

**Supplementary Table 5**

**Association of T0 A) FA and B) MD C) RD maps with clinical response (ΔHAMD) masked by the longitudinal ECT results mask. Cluster, MNI coordinates, peak voxel.**

1. Positive association of FA and ΔHAMD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 58 | 0.975 | 15 | -7 | -4 |
| 16 | 0.958 | 34 | -6 | -12 |
| 2 | 0.95 | 20 | -13 | 2 |

1. Negative association of MD and ΔHAMD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 213 | 0.991 | 47 | -18 | -19 |

1. Negative association of RD and ΔHAMD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Voxels | MAX 1-p | MNI X (mm) | MNI Y (mm) | MNI Z (mm) |
| 172 | 0.98 | 48 | -17 | -20 |

FA = fractional anisotropy; MD = mean diffusivity; RD= radial diffusivity; HAMD = sum score of the Hamilton depression scale; ΔHAMD = Difference Score (HAMDT0 – HAMDT1), high positive score reflects a good clinical response

On the top dimensions of clusters (number of voxels) and localization of signal peaks (MNI coordinates) are given for regions showing maximal differences of tract-based spatial statistics values (signal peak).

References for Supplementary Material

**Gardner DM, Murphy AL, O’Donnell H, Centorrino F, Baldessarini RJ** (2010). International consensus study of antipsychotic dosing. *American Journal of Psychiatry* **167**, 686–693.

**Redlich R, Almeida JRC, Grotegerd D, Opel N, Kugel H, Heindel W, Arolt V, Phillips ML, Dannlowski U** (2014). Brain morphometric biomarkers distinguishing unipolar and bipolar depression: a voxel-based morphometry-pattern classification approach. *JAMA Psychiatry* **71**, 1222–30.