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van Waarde, J.A.; Scholte, H.S.; van Oudheusden, L.J.B.; Verwey, B.; Denys, D.; van Wingen, G.A.

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ORIGINAL ARTICLE

A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression

JA van Waarde[1], HS Scholte[2], LJB van Oudheusden[1], B Verwey[1], D Denys[3] and GA van Wingen[3]

Electroconvulsive therapy (ECT) is effective even in treatment-resistant patients with major depression. Currently, there are no markers available that can assist in identifying those patients most likely to benefit from ECT. In the present study, we investigated whether resting-state network connectivity can predict treatment outcome for individual patients. We included forty-five patients with severe and treatment-resistant unipolar depression and collected functional magnetic resonance imaging scans before the course of ECT. We extracted resting-state networks and used multivariate pattern analysis to discover networks that predicted recovery from depression. Cross-validation revealed two resting-state networks with significant classification accuracy after correction for multiple comparisons. A network centered in the dorsomedial prefrontal cortex (including the dorsolateral prefrontal cortex, orbitofrontal cortex and posterior cingulate cortex) showed a sensitivity of 84% and specificity of 85%. Another network centered in the anterior cingulate cortex (including the dorsolateral prefrontal cortex, sensorimotor cortex, parahippocampal gyrus and midbrain) showed a sensitivity of 80% and a specificity of 75%. These preliminary results demonstrate that resting-state networks may predict treatment outcome for individual patients and suggest that resting-state networks have the potential to serve as prognostic neuroimaging biomarkers to guide personalized treatment decisions.

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INTRODUCTION

Depression is the leading cause of disability worldwide and is a major contributor to the global burden of disease.[1,2] Successful treatment is possible using psychotherapeutical, psychopharmacologic or combined strategies. Despite adequate treatment, about 30% of patients remain depressed.[3] In more severe and treatment-resistant cases, electroconvulsive therapy (ECT) under general anesthesia and with the use of adequate muscle relaxation may be very effective.[1] Although 48–65% of the depressed patients recover with ECT, this treatment frequently provokes cognitive adverse effects and may be regarded as more invasive than pharmacotherapy.[1,4–7] Moreover, as treatment with ECT generates costs for hospitals, financial considerations may limit its availability.[8] However, for severely suicidal and/or somatically compromised patients, ECT may be a life-saving procedure in which the benefits substantially outweigh both the costs and adverse effects.

Although clinical characteristics such as disturbances in vegetative functions, psychomotor retardation, psychotic features, heritability and shorter duration of illness have been used to predict the outcome of ECT,[1,9–11] there is a lack of objective and reliable evidence on which to base the selection of patients suitable for ECT. Preferably, a reliable prediction tool should produce individualized results, as only this will adequately allow the clinician to inform the patient and realistically support the individual decision-making process. In this way, the chance to recover from depression can be weighed against the risk of possible cognitive adverse effects and the unnecessary costs of ineffective treatment might be avoided.

Using noninvasive methods such as functional magnetic resonance imaging (fMRI), researchers aim to develop robust diagnostic and prognostic classifiers for individual patients. Recent studies have started to use machine-learning techniques; these refer to a group of statistical methods used to detect patterns or regularities within high-dimensional data such as fMRI.[12] These methods can distinguish between depressed patients and healthy controls with a very high accuracy ($>94\%$) at the individual patient level by using functional connectivity data obtained during rest.[13,14] Furthermore, the preliminary results of two small studies indicate the possibility of classifying patients at baseline as either remitter or non-remitter before undergoing antidepressant treatment (fluoxetine; $n=19$)[15] or cognitive behavioral therapy ($n=16$).[16]

Clinically speaking, to inform the patient more accurately and to assess the advantages and disadvantages of ECT with greater precision, identification of a patient as a probable remitter or non-remitter in advance of ECT would be valuable. In this pilot study, we therefore used a machine-learning method to examine the prognostic value of pre-ECT resting-state fMRI in patients with severe and/or treatment-resistant unipolar depression.

[1]Department of Psychiatry, Rijnstate Hospital, Arnhem, The Netherlands; [2]Cognitive Neuroscience Group, University of Amsterdam, Amsterdam, The Netherlands and [3]Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. Correspondence: Dr JA van Waarde, Department of Psychiatry, Rijnstate Hospital, PO Box 9555, 6800 TA Arnhem, The Netherlands or Dr GA van Wingen, University of Amsterdam, Academic Medical Center, Department of Psychiatry, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands.
E-mail: jvanwaarde@rijnstate.nl or guidovanwingen@gmail.com
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PATIENTS AND METHODS

Participants

Resting-state fMRI data were available from a prospective observational study relating ECT outcome to structural MRI data, including patients indicated for ECT in the Rijnstate Hospital in Arnhem, the Netherlands (a 36-bed psychiatric facility with a catchment area of 600 000 inhabitants) from 2009 to 2011.[17,18] We included patients suffering from severe and/or treatment-resistant unipolar depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) as diagnosed by at least two independent experienced psychiatrists. A course of ECT was indicated for all patients ($n = 45$). Age, sex, previous ECT treatment and total administered ECT sessions during the course and concomitant medication use were documented. We scored the severity of depression in the week before the first ECT session (baseline) and within 1 week after the last ECT session using the Montgomery–Åsberg Depression Rating Scale (MADRS). This is a validated observer-rated scale with 10 items (scored 1–6 per item), with higher scores indicating increasingly severe depressive symptoms.[19] Patients with a final MADRS score $\leqslant 10$ at end point were considered to be in complete remission ('remitters'; $n = 25$), and the remaining patients were considered to be 'non-remitters' ($n = 20$).[20]

The local Medical Ethical committee approved the study protocol and after a complete description of the study to the subjects, we obtained written informed consent from all participants (Registration number: NL24697.091.09).

Electroconvulsive therapy

ECT was administered using a constant current (0.9 A), (ultra-) brief pulse (0.25 ms in right unilateral ECT (RUL) and 0.5 ms in bifrontotemporal (BL)) ECT device (maximum output 1008 mC; Thymatron IV; Somatics Incorporation, Lake Bluff, IL, USA), after induction of anesthesia intravenously with etomidate (0.2–0.5 mg kg^{-1} body mass), muscle paralysis with succinylcholine (0.5–1 mg kg^{-1} body mass) intravenously and with appropriate oxygenation (100% oxygen, positive pressure) until the resumption of spontaneous respiration. Electrode placement was started RUL ($n = 37$; 82%), except in patients at high risk for suicidal behavior and/or somatic complications, or in cases where previous ECT had been successfully administered bilaterally. Initial seizure threshold was measured at the first ECT session by an empirical titration method[17] and the consecutive electrical dosage was then set at 6 times initial seizure threshold in RUL ECT and at 2.5 times initial seizure threshold for BL treatment. ECT was administered two times a week. RUL electrode placement was changed into BL during the ECT course, based on the clinical decision of experienced psychiatrists. Generally, this occurred if the patient did not show (sufficient) improvement after six RUL sessions ($n = 22$; 49%). The index course of ECT was terminated or continued on a lower frequency if the patient had recovered (MADRS score $\leqslant 10$) or showed no (further) clinical improvement over a period of 2 weeks, or had shown no improvement at all after 10 BL sessions, based on the judgment of at least two independent experienced psychiatrists.

Structural and functional MRI

Within 2 weeks before the first ECT session, a structural and functional MRI of the head was made. Imaging was performed on a 1.5 T Philips MRI scanner (Philips, Best, The Netherlands), using an 8-channel SENSE head coil. The scanning protocol included a high-resolution T1-weighted turbo field echo MRI (sequence parameters: repetition time = 7.6 ms; echo time = 3.5 ms; flip angle = 15°; 145 sagittal slices; voxel size = 1.1 mm isotropic). For fMRI, using blood oxygen level-dependent signals, two-dimensional gradient-echo single-shot echoplanar imaging was used to acquire T2*-weighted MRI volumes (sequence parameters: repetition time = 1868 ms; echo time = 30 ms; flip angle = 90°; slice thickness = 4.5 mm; field of view = 230 mm; 96 × 96 matrix; 150 volumes).

Preprocessing and independent component analysis

Functional data were analyzed using FSL (http://fsl.fmrib.ox.ac.uk/fsl/) and the following processing steps were applied: removal of non-brain tissue, motion correction, spatial smoothing with a Gaussian kernel of 6 mm full-width at half-maximum, grand mean intensity normalization, high-pass temporal filtering (sigma = 75 s), linear registration to Montreal Neurological Institute space using coregistration to the high-resolution T1 scan, and resampling into 4 mm isotropic voxels to limit the number of voxels for subsequent processing steps. Standard group independent component analysis was then performed to obtain physiologically meaningful resting-state networks and reduce dimensionality of the data using Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC), including data demeaning and variance normalization.[21] All data sets were concatenated in time and dimensionality was estimated automatically, resulting in 32 independent components. Dual regression was used to obtain subject-specific expressions of each component. Components reflecting non-neural signals (e.g., motion, white matter, cerebral spinal fluid) were removed, and the remaining 25 network images were maintained for further analysis.

Structural data were analyzed using voxel-based morphometry (VBM) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Gray matter images were obtained from the structural scans using segmentation and were subsequently normalized to Montreal Neurological Institute space using modulation to obtain regional volume images. The images were then resampled to 2 mm isotropic voxels to limit the number of voxels for subsequent processing steps, and also to retain sufficient high-resolution anatomic information. The images were also smoothed with a Gaussian kernel of twice the voxel size (4 mm full-width at half-maximum).

Pattern classification

To assess whether resting-state networks or structural data could predict remission or non-remission from depression, each network and voxel-based morphometry image was entered into a supervised multivariate classification procedure using a linear support vector machine (SVM) algorithm (Figure 1; http://www.csie.ntu.edu.tw/~cjlin/libsvm/). The SVM classifier was trained and tested using leave-one-per-group-out cross-validation with 19 subjects per group to avoid bias to the largest group. During the training phase, a hyperplane was estimated that maximally separates the remitters from the non-remitters based on all available data points (features) that showed a difference between the groups. We then tested the accuracy with which the determined hyperplane could classify other subjects during the classification stage with independent data not used for training. For each cross-validation iteration and evaluation of the accuracy of the classifier, we excluded a random participant from the non-remitters and six subjects from the remitters to keep both groups of equal size during the training stage. A data-driven feature-selection procedure was applied by averaging the group members per voxel, subtracting the groups from each other and transforming the resulting values in *z*-scores. Three separate classification analyses were performed with *z*-thresholds at 3, 3.5 and 4. As this feature selecting depends strongly on the incidental inclusion of subjects, and because we wanted to obtain information about the reliability of the classification procedure at a group level, this procedure was iterated 10 000 times for each network and *z*-threshold.

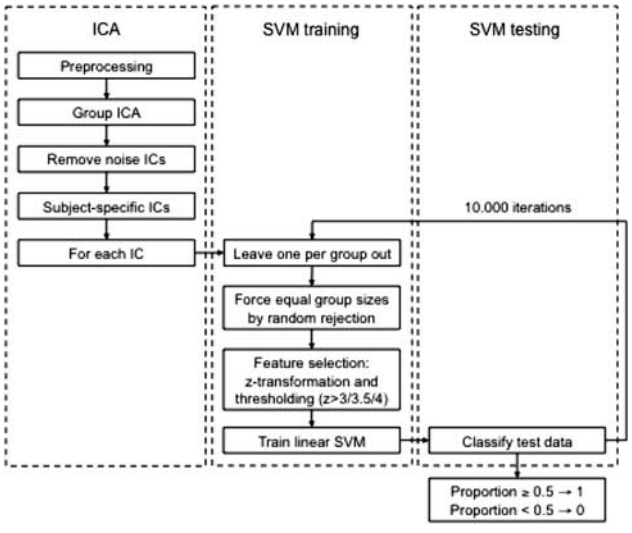

Figure 1. Flow diagram illustrating the independent component analysis (ICA) and support vector machine (SVM) classification procedure of resting-state functional magnetic resonance imaging (MRI) data.

Table 1. Characteristics of 45 patients undergoing a course of ECT assessed with functional MRI, and grouped according to their post-ECT MADRS score as remitter or non-remitter

Patient characteristics	*All* (n = *45*)	*Remitter post-ECT MADRS score* ⩽ *10* (n = *25*)	*Non-remitter post-ECT MADRS score* > *10* (n = *20*)	P-*value comparison remitters and non-remitters*
Mean age ± s.d. (in years)	56.6 ± 14.1	59.8 ± 13.7	52.6 ± 14.0	0.09[a]
Female sex (%)	28 (62)	16 (67)	12 (57)	1.00[b]
Diagnosis of depressive disorder (%)	45 (100)			
Without psychotic features (%)	35 (78)	17 (68)	18 (90)	0.15
With psychotic features (%)	10 (22)	8 (32)	2 (10)	
Mean MADRS score ± s.d.				
At baseline	36.5 ± 8.3	36.9 ± 7.9	36.1 ± 9.0	0.73[a]
After ECT course	13.1 ± 10.4	5.6 ± 3.0	22.4 ± 8.6	< 0.001[c]
MADRS score ⩽ 10 point after ECT ('remitter')	25 (56)			
MADRS score decreased ⩾ 50% after ECT ('responder')	31 (69)			
Treatment characteristics				
Previous ECT treatment (%)	12 (27)	9 (36)	3 (15)	0.18[b]
Total administered ECT sessions during the course ± s.d.	18.7 ± 7.1	17.6 ± 7.6	20.1 ± 6.4	0.26[a]
Use of concomitant psychopharmacologic drugs				
Benzodiazepines (%)	29 (64)	17 (68)	12 (60)	0.76[b]
Antidepressants (%)	29 (64)	17 (68)	12 (60)	0.76[b]
Antipsychotics (%)	29 (64)	17 (68)	12 (60)	0.76[b]
Antiepileptics (%)	1 (2)	0 (0)	1 (5)	0.44[b]

Abbreviations: ECT, electroconvulsive therapy; MADRS, Montgomery–Åsberg Depression Rating Scale. [a]Independent samples *t*-test. [b]Fisher's exact test. [c]Mann–Whitney *U*-test.

This resulted in an accuracy measure, per subject, based on the number of times the subject was included in the test sample and correctly classified. When the proportion of classifications was ⩾0.5, the subject was considered correctly classified. Statistical significance was determined by binomial test with Bonferroni correction for all networks and feature-selection models. A map of the brain regions with the largest contribution to the classification results was generated by an inverse independent component analysis.

Univariate data analysis

To evaluate whether significant multivariate pattern classifiers resonated consistent univariate differences in connectivity between groups, we performed additional univariate two-sample *t*-tests. Permutation tests were carried out with family-wise error rate correction for multiple voxel-wise comparisons ($P < 0.05$) using threshold-free cluster enhancement[22] with 5000 permutations implemented in FSL.

Statistical analysis of clinical data

Data are presented as means ± s.d. or numbers and percentages when appropriate. The group of remitters ($n = 25$) was compared with the non-remitters ($n = 20$) using *t*-tests or Mann–Whitney *U*-tests when appropriate (age, MADRS scores and total administered ECT sessions) and Fisher's exact tests (sex, presence of psychotic features, previous ECT treatment and concomitant medication used) for dichotomous variables. Mean pre- and post-ECT MADRS scores were compared using a paired *t*-test. All tests were two-sided, with $P < 0.05$ denoting statistical significance; SPSS for Windows (version 20) was used for all analyses.

RESULTS

Study participants

Data of 45 patients with unipolar depression (mean age 56.6 ± 14.1 years; 28 (62%) female; mean MADRS score at baseline 36.5 ± 8.3) were available for the analyses. On average, we administered a total of 18.7 ± 7.1 ECT sessions to the patients during a completed treatment course. These patients did not differ from the total group of patients indicated for ECT and which participated in the original observational study.[17] After ECT, the mean MADRS score in the total group was significantly lower than pre-ECT (mean post-ECT MADRS score: 13.1 ± 10.4; $P < 0.001$) and had decreased (on average) by 23.4 ± 12.9 points. After ECT, the MADRS scores decreased ⩾ 50% in 69% ($n = 31$) of all patients, and 56% ($n = 25$) reached complete remission. Per definition, the MADRS scores were significantly lower in the remission group than in the non-remission group ($P < 0.001$) after completion of the ECT course. However, there were no significant differences in the baseline MADRS scores, age, sex, presence of psychotic features, presence of previous ECT course(s), total number of ECT sessions or concomitant medications, thus indicating that no clinical data included in these analyses were available that might have predicted remission at the group level (all $P > 0.05$) (Table 1).

Differences in movement within the scanner between the group of remitters and non-remitters could generate artifacts in the fMRI signal, causing long-range correlations that could be mistaken for connectivity changes, which in turn could be linked to response. We therefore examined head motion during scanning, but this revealed no significant differences in mean head displacement between the remitters and non-remitters (absolute displacement: $P = 0.24$; relative displacement: $P = 0.17$).

fMRI prediction of ECT outcome

Two resting-state networks showed significant classification accuracy after correcting for multiple comparisons. The first network (centered in the dorsomedial prefrontal cortex and including the dorsolateral prefrontal cortex, orbitofrontal cortex and posterior cingulate cortex) had a sensitivity of 84% (the proportion of correctly classified remitters) and a specificity of 85% (the proportion of correctly classified non-remitters) to predict whether a patient would remit from depression (Figure 2). This network had a positive predictive value of 88%, which is the proportion of true-positive test results. The second network (centered in the anterior cingulate cortex and including the

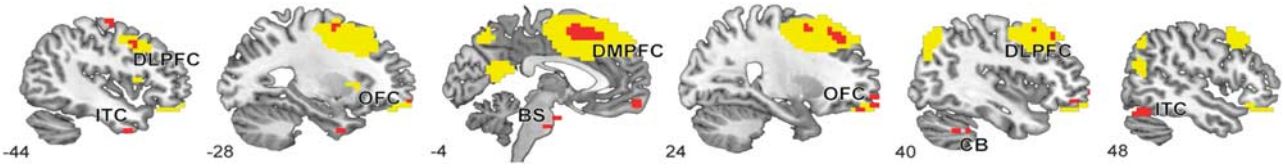

Figure 2. The first resting-state network that predicted remission from depression. The features that showed accurate classification of remitted and non-remitted patients are shown in red, superimposed on the network that was used for classification in yellow ($z > 2.3$). The panels present the results from the left side of the brain to the right side (x coordinates in Montreal Neurological Institute space). BS, brainstem; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ITC, inferior temporal cortex; OFC, orbitofrontal cortex.

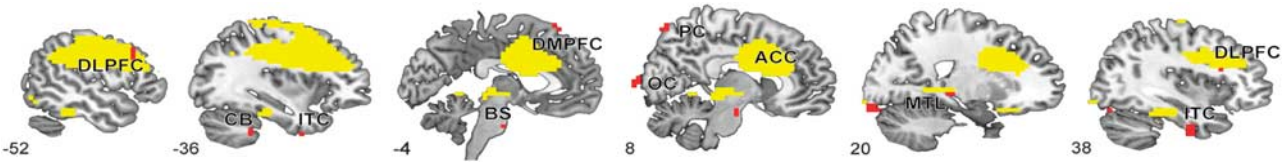

Figure 3. The second resting-state network that predicted remission from depression. The features that showed accurate classification of remitted and non-remitted patients are shown in red, and superimposed on the network that was used for classification in yellow ($z > 2.3$). The panels present the results from the left side of the brain to the right side (x coordinates in Montreal Neurological Institute space). ACC, anterior cingulate cortex; BS, brainstem; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ITC, inferior temporal cortex; MTL, medial temporal lobe; OC, occipital cortex; PC, parietal cortex.

dorsolateral prefrontal cortex, sensorimotor cortex, parahippocampal gyrus and midbrain) had 80% sensitivity, 75% specificity and 80% positive predictive value for remission (Figure 3). The prediction accuracy based on structural gray matter images was 61%, which was nonsignificant.

Since the presence of psychotic symptoms is currently the best clinical predictor available for ECT at group level (although not significant in our data[17]), we assessed whether the classification remained accurate even after the exclusion of psychotically depressed patients ($n = 10$). The sensitivity of the first network increased slightly to 88%, with 83% specificity and a positive predictive value of 83%. The sensitivity of the second network decreased slightly to 76%, with 72% specificity and a positive predictive value of 72%. Thus, the classification of remission was not derived from the distinction between psychotically and non-psychotically depressed patients.

To evaluate whether these two resting-state networks also showed consistent univariate differences in connectivity between groups in specific brain regions, we carried out additional two-sample *t*-tests. These tests revealed no observable significant differences in connectivity between the remission and non-remission groups after correction for multiple comparisons ($P > 0.05$).

DISCUSSION

This prospective pilot study reveals that the whole brain pattern of neural connectivity distinguished between patients who reached complete remission following a course of ECT and patients who did not. The sensitivity of two baseline resting-state fMRI networks for estimating remission after ECT was 80% and higher with similar specificity. For a marker to be considered clinically useful, it is generally required to show 80% sensitivity and specificity.[12]

The brain areas that provided the largest contribution to the classification of remitters versus non-remitters were the cingulate cortex and the medial- and orbitofrontal cortices (Figures 2 and 3). Increased activation in these brain regions is associated with response to pharmacotherapy and cognitive behavioral therapy in less severely depressed patients.[23] Note that not all predictive brain areas were located within the analyzed networks, which suggests that the brain regions not strongly correlated to the network of interest do show discriminative properties. This can be understood as relative decoupling of these brain regions with the network of interest, or by appreciating the multivariate nature of the results that do not need to overlap with the univariate connectivity network maps, indicating that these regions are only part of a multidimensional network. Interestingly, the dorsomedial prefrontal cortex appears to serve as a hub of multiple networks implicated in depression.[24,25] Neuroimaging studies investigating neural changes associated with ECT also indicate involvement of the dorsomedial prefrontal, dorsolateral prefrontal, anterior cingulate and orbitofrontal cortices.[26–29] Although our findings underscore the key role of the prefrontal cortex in the antidepressive response as found by others, our results differ due to their multivariate nature. As such, the results do not reflect increased or decreased connectivity in particular brain regions. In fact, the univariate analyses showed no consistent group differences in regional connectivity strength. This suggests that the predictive markers are based on a distinct pattern of connectivity across many nodes of these networks in patients that remit after ECT. This also implies that the results are not readily explicable in simpler terms, which may hamper the interpretation of the results in physiologic terms. Although this difficulty may limit the credibility of this technique, this seems inherent to the methodology. The differences in sensitivity may also partly explain the divergent results of the mutivariate and univariate analyses. Univariate analyses that test thousands of independent voxels in parallel require stringent correction for multiple comparisons to control for false-positive results, whereas no such correction is necessary for multivariate methods that combine all the included data.

The results showed that the structural data had no predictive value. This is at odds with a small pilot study that showed that structural data could predict remission from depression after fluoxetine treatment in 18 non-treatment-resistant patients with 89% accuracy.[30] A more recent study with a larger sample size showed a 70% accuracy in predicting the response to various antidepressants, which was significant, but below the accuracy

considered clinically useful.[31] It may be argued that our study with a sample of treatment-resistant patients and a different treatment modality (ECT versus antidepressants) differs too much from these other studies, but together these studies suggest that structural data do not yet provide sufficient information for predicting treatment response in depression. As depression and other neuropsychiatric disorders are characterized by differences in functional connectivity,[32] resting-state connectivity may provide a more sensitive measure to discover MRI markers.

Electrode placement determines the intracerebral spatial distribution of electrical charge density and thereby determines the resultant initiation of seizure activity. For ECT to be effective, it is hypothesized that seizures need to be initiated in the prefrontal areas and that the mechanism of therapeutic action of ECT may be related to the suppression of functional brain activity, especially in the prefrontal cortex.[33–35] Remarkably, our predicting networks include prefrontal brain areas directly beneath the electrodes, supporting the hypothesis that direct electrical stimulation in these prefrontal areas is crucial for seizure initiation and ECT effectiveness. The 'anatomico-ictal theory' of the working mechanism of ECT may explain the involvement of more deeply located brain areas in our predictive networks (such as the brainstem, midbrain and cingulate cortex). This theory states that the greatest antidepressive impact of ECT is achieved when seizures are initiated in the prefrontal regions and then propagated maximally throughout the cortex and subcortex, involving diencephalic centers in particular.[33,36]

Clinical implications

Despite the fact that the present pilot study used an internal validation method, the results should be replicated in an independent cohort to justify that the neuroimaging marker we identified is robust against both technical (e.g., data acquisition) and clinical variations. When replicated, these results may help clinicians, patients and their significant others to make better-informed treatment decisions. The remission rate of ECT generally ranges from 48 to 65% [7] and was 56% in the present study. Thus, about half of our patients did not derive optimal benefit from the ECT and were possibly exposed to unnecessary cognitive adverse effects and costs.[1] On the other hand, we classified remission/non-remission defined as a MADRS score $\leqslant 10$ at end point, which from a clinical perspective may be too strict a criterion, because in several patients even a partial response to ECT would be beneficial.

Our data set derived from a prospective study, in which 91 out of 114 patients (80%) indicated for ECT agreed to participate and underwent the fMRI procedure.[18] We therefore think that 5 min of resting-state fMRI is achievable in daily clinical practice, even in severely ill, psychotically depressed patients. Pre-ECT fMRI data as a marker for treatment efficacy may help to guide clinicians in their discussions with patients and relatives in ascertaining the expectations related to this treatment and in turn may lead to greater cost effectiveness.

Study limitations

In general, the heterogeneity within a given clinical diagnosis is a warning for any appropriate marker. In our sample of patients with unipolar depression, this may not be problematic because the patients formed a highly selected group, that is, they were indicated for ECT by at least two independent experienced clinicians. As we only examined patients with unipolar depression in this study, our results cannot be generalized to the entire ECT population. We cannot exclude however that different brain processes are involved here as opposed to other (e.g., bipolar) depressive patient groups. Furthermore, most patients used a constant dose of concomitant medication(s) during the ECT course, which may have influenced undefined fMRI signals.[37] In our naturalistically studied ECT population, discontinuation of psychotropic medication was generally undesirable owing to the patients' illness; this suggests that our findings are representative for the regular ECT patient group.

Technical aspects such as hardware and acquisition parameters may have influenced the results. Although resting-state analyses appear robust against variations in data acquisition and pooling of data acquired at multiple sites is feasible,[38,39] the machine-learning procedure may have led to overfitting of the SVM classifiers with idiosyncratic features of the data, for instance, idiosyncrasies related to hardware and acquisition parameters and particular sample characteristics. This is inherent to the procedure as the test data left out during training are still more similar to the training data than to any potentially unseen data. Replication of our results in independent samples recruited in very different circumstances (i.e., a multisite study) is desirable, before more firm conclusions can be drawn.

Another possible drawback is that limited accessibility of MRI scanners may hamper general application of our brain biomarker predicting response to ECT. However, ECT is currently accessible in second- or third-line treatment hospitals in which MRI scanners are readily available.

In conclusion, this pilot study demonstrates that resting-state connectivity patterns in prefrontal and cingulate cortex networks are capable of predicting ECT efficacy in severe and treatment-resistant unipolar depressive patients. Application of this fMRI method can be examined in other psychiatric and neurologic conditions to discover further resting-state biomarkers for treatment response. Accurate prediction of treatment efficacy can be helpful to prevent unnecessary adverse effects and reduce health-care costs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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