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Effective resting-state connectivity in severe unipolar depression before and after electroconvulsive therapy

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depressive disorders. A recent multi-center study found no consistent changes in correlation-based (undirected) resting-state connectivity after ECT. Effective (directed) connectivity may provide more insight into the working mechanism of ECT.

Objective: We investigated whether there are consistent changes in effective resting-state connectivity.

Methods: This multi-center study included data from 189 patients suffering from severe unipolar depression and 59 healthy control participants. Longitudinal data were available for 81 patients and 24 healthy controls. We used dynamic causal modeling for resting-state functional magnetic resonance imaging to determine effective connectivity in the default mode, salience and central executive networks before and after a course of ECT. Bayesian general linear models were used to examine differences in baseline and longitudinal effective connectivity effects associated with ECT and its effectiveness.

Results: Compared to controls, depressed patients showed many differences in effective connectivity at baseline, which varied according to the presence of psychotic features and later treatment outcome. Additionally, effective connectivity changed after ECT, which was related to ECT effectiveness. Notably, treatment effectiveness was associated with decreasing and increasing effective connectivity from the posterior default mode network to the left and right insula, respectively. No effects were found using correlation-based (undirected) connectivity.

Conclusions: A beneficial response to ECT may depend on how brain regions influence each other in networks important for emotion and cognition. These findings further elucidate the working mechanisms of ECT and may provide directions for future non-invasive brain stimulation research.

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1. Introduction

With more than 250 million people affected, depression is one of the leading causes of disability worldwide [1]. Patients suffer weeks to sometimes years of low mood, anhedonia, sleep problems, weight loss, and — in more severe cases — suicidality, motor retardation and psychotic features. Although 70% of patients show a positive response to extensive treatments with pharmacotherapy and psychotherapy [2], approximately half of them eventually relapse and experience one or more recurrent episodes in their lifetime [2,3]. Patients suffering from severe depressive episodes that are not responsive to initial treatments may benefit from electroconvulsive therapy (ECT). With a remission rate of 48–65%, ECT is currently the most effective treatment for pharmacotherapy-resistant depression [4]. Nevertheless, it is clear that for a substantial group of depressed patients an effective treatment is still lacking. Enhancing our understanding on the neural mechanisms of depression and its treatments is indispensable to improve treatment effectiveness and to develop novel treatments.

The neural correlates of depression and its treatment with ECT have been studied extensively using structural magnetic resonance imaging (MRI) [5,6], functional MRI (fMRI) [7,8] and electroencephalography (EEG) [9,10]. Studies using fMRI have used correlation-based connectivity measures and have focused on the default mode network (DMN), salience network (SN) and central executive network (CEN). Due to their importance in psychopathology, these networks and their modes of interaction were incorporated into a 'triple network model' of psychopathology [11]. This model is also proposed to be of key importance for the etiology of depression [7,12]. However, despite multiple small scale studies reporting changes in prefrontal cortex connectivity after ECT, a recent multicenter study found no evidence for changes in functional connectivity after ECT [13]. This suggests that functional connectivity changes are not consistent across different samples.

One drawback of correlation-based connectivity is that it assumes undirected connections between regions of interest. Alternative methods have been developed that focus on effective connectivity, a measure of the extent to which one neural system exerts influence over another (e.g., how region A influences region B, in contrasts with mere correlations between time series of region A and B [14];. Dynamic causal modeling (DCM) is one of the most common of such methods, which uses a generative neural-mass model to infer effective (i.e., directed) connections between brain regions. Recent developments of DCM have enabled exploration of relatively large-scale networks [15] and longitudinal analyses.

Studies on effective connectivity reported widespread effective connectivity correlates associated with depression during task and resting-state fMRI [16–19]. With respect to depressed patients treated with ECT, only a few studies have examined effective connectivity correlates. Those studies have identified increased connectivity from a cerebellar region to the subgenual anterior cingulate cortex [20], and from the fusiform face area to the amygdala [21] following ECT. Additionally, another study found that effectiveness of ECT was associated with an increase in connectivity from the dorsolateral prefrontal cortex to the angular gyrus after ECT [22]. These studies were, however, limited to only a few regions of interest and small sample sizes.

In this present multicenter study, we used spectral DCM of resting-state fMRI (RS-fMRI) data to investigate effective connectivity between fourteen regions of the triple network model. Our primary analyses assessed whether there are consistent changes in effective connectivity after treatment with ECT and whether this is related to treatment response. Additionally, we performed secondary analyses to investigate whether there are consistent differences at baseline between patients with severe depression and healthy controls, between patients with and without psychotic features, and whether there were consistent associations with later treatment outcome. This study included the same samples as previous analysis [13], which did not show any changes in "regular" correlation-based functional connectivity or associations with clinical effectiveness.

2. Methods

2.1. Participants and treatment

Data were obtained from the Global ECT-MRI Research Collaboration (GEMRIC) [23]. All patients in this study were indicated for ECT and were treated according to internationally accepted guidelines. The data used for this study were acquired at seven sites across Europe and North America. All contributing sites received ethics approval from their local ethics committee or institutional review board. In addition, approval for the centralized mega-analysis was given by the Regional Ethics Committee South-East in Norway (No. 2018/769). All patients had a clinical diagnosis of unipolar major depressive disorder, classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Two of the seven sites provided neuroimaging data for healthy controls at baseline, one site provided longitudinal neuroimaging data for healthy controls. Some sites strictly studies predictive biomarkers and therefore only provided baseline data. Descriptive data on demographics (age, sex), baseline clinical (depression severity, presence of psychotic features), treatment (number of administered ECT-sessions during the course) and outcome (depression severity after the ECT-course, response [i.e., post-ECT >50% reduction of depression severity score], remission [i.e., post-ECT depression severity score <7]) variables were available. Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D) or Montgomery-Åsberg Depression Rating Scale (MADRS), depending on the sites' preferences. Ratings of the MADRS were converted to HAM-D scores [24], using the following formula:

$$HAMD = -1.58 + 0.86 * MADRS.$$

To create a more homogeneous sample, patients were excluded if bipolar disorder was present. Additionally, patients were excluded if neuroimaging data were unavailable or of insufficient quality.

2.2. fMRI acquisition and preprocessing

Structural and RS-fMRI data were acquired within two weeks before, and approximately one week after the ECT-course (for scanning parameters per site, see Supplementary Table 1). For healthy controls, the test-retest time was approximately 5 weeks. The fMRI preprocessing steps were identical for each participant. First, structural and functional images were reoriented and brain extraction was performed using Advanced Normalization Tools (ANTs v2.2.0). Images were coregistered using ANTs and FMRI Software Library (FSL v5.0.10) using boundary-based registration. After discarding the first two volumes for each fMRI series, FSL's MCFLIRT was used to apply head movement correction by realigning the volumes to the middle volume using six parameters for rigid body transformations. Functional images were spatially smoothed using a Gaussian kernel with 5 mm full-width at half-maximum. For motion correction, an ICA-based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA) was used. The noise components estimated by ICA-AROMA were used to compute denoised cosines for high pass filtering (f = 0.009). Furthermore, mean white matter (WM) and cerebrospinal fluid (CSF) timeseries were computed as additional nuisance variables. Temporal high-pass filtering was used to remove low-frequency drifts (<0.01 Hz) and images were registered to 4 mm isotropic voxel size. Both the denoised cosines and WM/CSF nuisance variables were used to denoise the fMRI data and perform high pass filtering in one single step [25]. ANTs were used for normalization of transformation matrices to Montreal Neurological Institute (MNI) space using 2 mm standard templates. Finally, the quality of the preprocessed images was assessed, and images with suboptimal quality were excluded from the analysis. The procedure for quality control is described in the supplementary information. Finally, RS-fMRI of

sufficient quality was available for a total of 248 participants with respect to cross-sectional baseline data. Regarding longitudinal data, RS-fMRI data of sufficient quality was available for 105 participants.

2.3. Statistical analysis

Spectral DCM (spDCM) for RS-fMRI was used to estimate effective connectivity parameters [26]. Analyses were conducted in Statistical Parametric Mapping (SPM12, revision 7771) with DCM12.5 (revision 7497). spDCM used a generative forward model with two components. The first one described how neuronal populations causally interact. The second component mapped neuronal activity from the first model to observed (cross-spectra of) hemodynamic responses. Thereby, spDCM was able to estimate directed connectivity between brain regions as well as regional self-connections. The construct validity of spDCM has been shown by its ability to accurately recover effective connectivity in simulated data [26,27], and specific effective connections corresponding to well-documented neural pathways in rodents [28].

A first-level spDCM analysis was performed on 14 regions of interest (ROIs; see Fig. 1), which comprise the core of the triple network model. Time series were extracted from a sphere with 5 mm radius centered around MNI coordinates extracted from previous research (Fig. 1 [29];. For analysis of baseline images, a spDCM analysis with default setting were used. For the longitudinal analysis, a multisession resting-state spDCM approach was used. For a detailed description of the first-level analysis procedure, see the supplementary information.

Group-level effects were estimated using Parametric Empirical Bayes (PEB) models [30]. A PEB general linear model (GLM) was used to infer effects at multiple levels (i.e., group effects or between-session effects) by combining the expected values and (co)variances from all individual-level spDCM parameters. PEB models were used to analyze the primary longitudinal effects associated with ECT and to analyze secondary group differences and associations with clinical characteristics at baseline. For each PEB model, the region-to-region effective connectivity was examined using Bayesian model reduction (BMR). This method compared model evidences for all possible reduced models (i.e., models with some connectivity parameters 'turned off' by fixing the prior probability to zero), and models with connectivity parameters that did not contribute to model evidence were iteratively discarded. This process was continued until removing parameters reduced the model evidence. Subsequently, a Bayesian model average was calculated over the 256 models with the largest model evidence in the final iteration. Using this 'pruning' and averaging approach allowed inference on the posterior probability of specific parameters. The specific PEB GLM models were adjusted for the following potentially confounding variables: age, sex, depression severity, medication use (antidepressants, benzodiazepines, and antipsychotics), psychotic features, electrode placement (only longitudinal analyses), number of ECT sessions (only longitudinal analyses), and site. A 99% posterior probability (pp) threshold was used. The (hyper)priors used in hierarchical Bayesian models such as these prevent overfitting and multiple comparison problems, therefore no corrections for multiplicity are applied [31,32]. In order to compare effective connectivity analyses with common resting-state analyses, correlation-based connectivity was investigated with mass univariate classical GLMs. An alpha of 0.05 was used for the latter analysis, Bonferroni corrected for multiple comparison.

3. Results

3.1. Sample and treatment

In total, 248 RS-fMRI baseline scans could be included (n = 189 patients; n = 59 healthy controls) in our analyses. For 105 participants, post-ECT scans were included (n = 81 patients; n = 24 healthy controls). The mean age for the total patient sample was 55.4 ± 15.8 SD, and 59% of the patient sample were female. Patients were severely depressed at baseline (mean HAM-D score 26.2 ± 7.2 SD). In the patient sample, 43 (23%) showed psychotic features at baseline. Most patients used concomitant pharmacotherapy during the ECT-course (61.4%), and patients without current use of pharmacotherapy did receive at least one trial of pharmacotherapy before. In the group of patients currently using antidepressants (AD), 34% used selective-serotonin reuptake inhibitors, 36% used selective-noradrenaline reuptake inhibitors, 27% used tricyclic antidepressants and 3% used monoamine oxidase inhibitors. Of the patients, 40% used concomitant benzodiazepines (BZ). Regarding used electrode placements, 126 patients received ECT with right unilateral (RUL) and 62 patients with a bilateral (BL) electrode placement. The average number of administered ECT-sessions per course was 12.4 ± 5.5 SD. For 13 patients post-ECT HAM-D scores were not available. After the ECT-course, mean HAM-D-score decreased significantly (post-ECT HAM-D 9.9 ± 8.1 SD; $p < 0.001$), 119 (68%) patients responded and 83 (47%) patients achieved remission. Patients that were included in the longitudinal analysis did not differ significantly from patients only included in baseline analysis with respect to age, sex, or change in HAM-D ($p > 0.05$ for all analyses). Patients only included in the baseline analysis did show slightly greater baseline HAM-D at trend level ($p = 0.06$). This was mainly due to one site that only acquired baseline scans and included more severely depressed patients.

3.2. Effective connectivity at baseline

A wide range of effective connectivity parameters showed differences between patients and healthy controls (pp > 0.99; Fig. 2). All analyses are adjusted for potential confounding variables such as

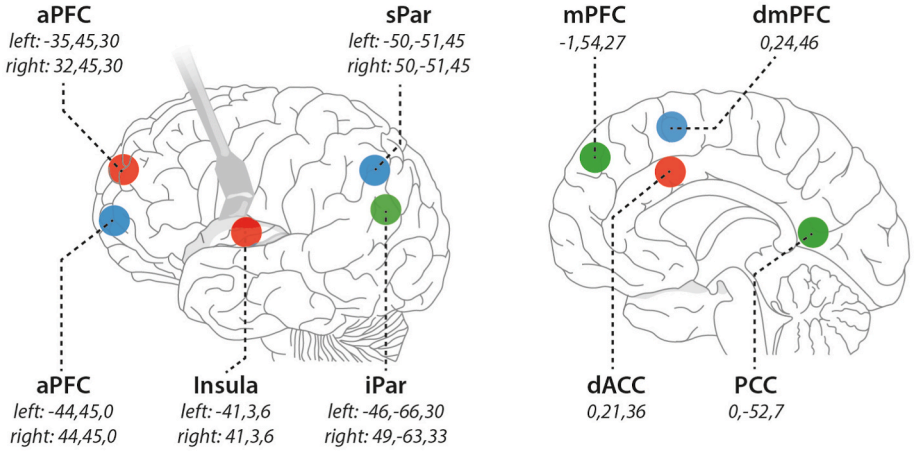

Fig. 1. Overview of the regions of interest with their respective MNI coordinates. The regions belong to three networks: the central executive network (blue), salience network (red), and default mode network (green). aPFC = anterior prefrontal cortex; sPar = superior parietal cortex; mPFC = medial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; iPar = inferior parietal cortex; dACC = dorsal anterior cingulate cortex; PCC = posterior cingulate cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

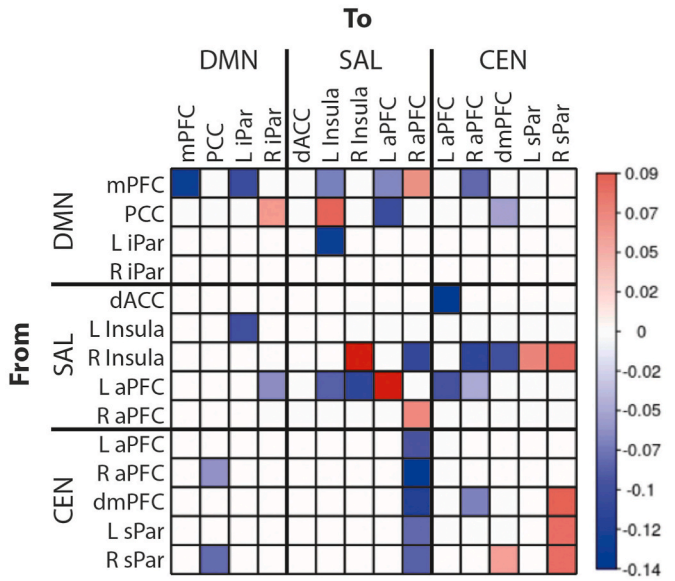

Fig. 2. Effective connectivity differences between patients with severe unipolar depression and healthy controls. For off-diagonal parameters (i.e., between region connectivity), red and blue indicate increased and reduced connectivity strength in depression compared to healthy controls, respectively. The units are in Hertz. For parameters on the diagonal (self-connections), red and blue indicate stronger and weaker self-inhibition compared to healthy controls, respectively. These parameters are in arbitrary units. The variance for each connectivity parameter shown here was < 0.01. For abbreviations, see Fig. 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

medication use (see Methods). Most notably, patients showed altered efferent (outgoing) connectivity from the medial prefrontal cortex (mPFC; DMN), the right insula (SN) and the left anterior PFC (aPFC; SN). Additionally, patients showed reduced excitation from all nodes of the CEN to the right aPFC (SN) compared to healthy controls. Patients showed increased connectivity from the right insula to posterior CEN regions, whereas reduced connectivity from right insula to anterior CEN. Moreover, patients showed greater self-inhibition in multiple regions of the SN compared to healthy controls, i.e., the bilateral aPFC and right insula. Analysis on effective connectivity correlates of depression severity did not yield any connections with sufficient evidence.

Analysis on differences between patients with and without psychotic features yielded strong evidence for group differences in 21 connectivity parameters (pp > 0.99; Supplementary Fig. 1). Among other connections, the presence of psychotic features was associated with increased excitation from multiple nodes of the SN to the left aPFC (CEN). Additionally, multiple nodes throughout different networks showed reduced self-inhibition in patients with psychotic features. Psychotic features were also associated with an inter-hemispheric connectivity pattern within the SN. Specifically, patients with psychotic features showed increased excitation from the left insula to the right insula, and from the left aPFC to the right aPFC.

Analyses on baseline effective connectivity correlates of ECT effectiveness (change in HAM-D; pp > 0.99; Supplementary Fig. 2), response (>50% change; Supplementary Fig. 3) and remission (post-ECT HAM-D≤7; Supplementary Fig. 4) revealed widespread associations throughout the brain. Parameters that were associated with all three of the effectiveness variables were increased connectivity from the dorsomedial PFC (dmPFC; CEN) to the dorsal anterior cingulate cortex (dACC; SN), and from the left insula (SN) to the right aPFC (SN).

The baseline models on correlation-based functional connectivity did not yield any significant results (p > 0.05, adjusted for multiple comparison for all connections).

3.3. Effective connectivity after ECT

To study the general effect of ECT, we examined longitudinal differences in effective connectivity between patients and healthy controls. The analysis yielded 12 connectivity parameters with longitudinal differences between groups (pp > 0.99). However, eight of these parameters showed strong evidence for differences between time points in healthy controls only, indicating that these reflect test-retest variability in the healthy control group. The other four parameters suggested that, after the ECT-course, patients had increased connectivity from the right inferior parietal cortex (iPar; DMN) to the right insula (SN), increased connectivity from the dmPFC (CEN) to the left iPar (DMN) and reduced connectivity from the left superior parietal cortex (sPar; CEN) to the left insula (SN). Additionally, patients showed reduced self-inhibition in the left aPFC (SN) after ECT (Fig. 3). This seems to reverse altered effective connectivity associated with depression in the baseline analysis (see increased self-inhibition in the left aPFC at baseline in Fig. 2).

Analyses on longitudinal connectivity correlates of ECT effectiveness (change in HAM-D) showed lateralized effects in the insula (pp > 0.99). Specifically, higher effectiveness was associated with increased connectivity after the ECT-course from the posterior parietal cortex (PCC; DMN) to the right insula (SN), and with reduced connectivity from the PCC (DMN) to the left insula (SN) (Fig. 4). Effective connectivity correlates of remission and response did not overlap with correlates of the continuous effectiveness measure. Both response and remission were associated with increased connectivity from the posterior DMN to the right aPFC (CEN) (pp > 0.99; Supplementary Figs. 5 and 6).

Multiple effective connectivity parameters were correlated with the number of administered ECT-sessions during the course (pp > 0.99). Among other parameters, strong evidence was found for an association between the number of ECT-sessions and decreased self-inhibition in the

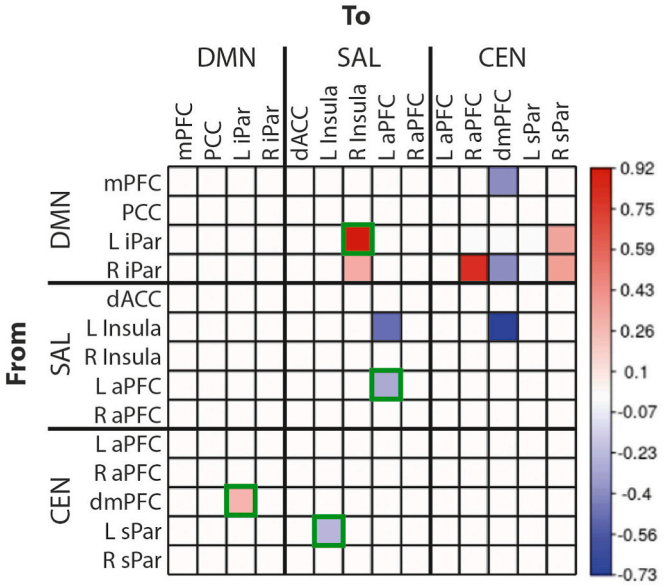

Fig. 3. Longitudinal changes in effective connectivity after electroconvulsive therapy (ECT). For off-diagonal parameters (i.e., between region connectivity), red and blue indicate increased and reduced connectivity strength in depression after ECT compared to longitudinal data in healthy controls, respectively (thresholded at pp > 0.99). The units are in Hertz. For parameters on the diagonal (self-connections), red and blue indicate stronger and weaker self-inhibition after ECT compared to longitudinal data in healthy controls, respectively. These parameters are in arbitrary units. Green squares indicate connectivity parameters that were not due to test-retest variability in the healthy control group. The variance for each connectivity parameter shown here was < 0.1. For abbreviations, see Fig. 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

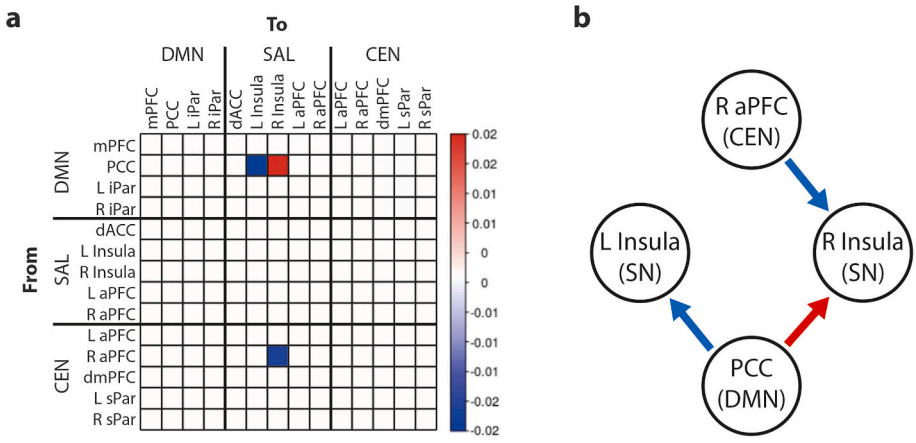

Fig. 4. Changes in effective connectivity after electroconvulsive therapy (ECT) associated with treatment effectiveness. (a) Red and blue, respectively, indicate increased and reduced connectivity after ECT associated with treatment effectiveness (thresholded at pp > 0.99). Effectiveness is measured in change in Hamilton Depression Rating Scale (HAM-D) score. The units are in change in Hertz after ECT per points change in HAM-D. The variance for each connectivity parameter shown here was < 0.003 For abbreviations, see Fig. 1. (b) a graphical representation of the findings in (a). Red and blue arrows, respectively, indicate increased and reduced connectivity after ECT associated with treatment effectiveness (thresholded at pp > 0.99). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

left aPFC (CEN and SN) after ECT (Supplementary Fig. 7).

Finally, effective connectivity was associated with unilateral versus bilateral electrode placement (pp > 0.99). Notably, unilateral electrode placement resulted in greater connectivity from the right insula (SN) to the dACC (SN) after treatment compared to bilateral electrode placement. Additionally, left to right insula (SN) effective connectivity showed greater increase in bilateral treatment (Supplementary Fig. 8).

The longitudinal models on correlation-based functional connectivity did not yield any significant results (p > 0.05, adjusted for multiple comparison for all connections).

4. Discussion

In this multi-center cohort study, we explored the effective resting-state connectivity correlates of severe depression and its treatment with ECT. The effective connectivity analyses yielded many cross-sectional and longitudinal effective connectivity correlates throughout the triple network model. This indicates that having a depression is associated with altered effective connectivity, and that ECT changes the influence from multiple brain regions in the triple network model to other nodes of these networks. In contrast, correlation-based functional connectivity analyses did not show any significant connectivity correlates. Severe depression at baseline was associated with altered efferent effective connectivity from core regions of the SN and DMN and increased self-inhibition in multiple regions of the SN. Whereas depressed status was associated with many effective connectivity parameters, analysis on depression severity did not reveal any associated parameters. Regarding treatment with ECT, treatment effectiveness was associated with decreasing and increasing effective connectivity from the PCC (DMN) to the left and right insula (SN), respectively. Greater connectivity between the PCC and the left insula at baseline was also associated with depressive status, response, and remission to ECT.

The results of this study suggest that patients suffering from severe depression are characterized by increased inhibition within multiple nodes of the SN, including the right insula. This possibly reflects a general down-regulation of activity in the SN in severely depressed patients. This is in line with previous findings, that showed reduced functional connectivity [33] and flexibility [34] within the SN in depressed patients. The SN, and the right insula in particular, has been put forward as a critical system for switching between the CEN and DMN [35,36]. This is proposed to underlie appropriate responses to salient stimuli by adaptively switching between task-oriented (supported by the CEN) and self-oriented attention (supported by the DMN) [11]. Additionally, the SN is thought to play a key role in emotion regulation, salience detection, and interoception [37,38]. Excessive inhibition of the SN may therefore underlie depressive phenotypes [39,40].

Previous studies showed decreased connectivity between the posterior DMN and CEN in patients suffering from depression (for a review, see Ref. [7]. Additionally, dynamic resting-state connectivity between the posterior DMN and the right nodes of the right CEN showed decreased variability in depression [48]. In line with this, our findings suggest reduced connectivity from the right CEN to the PCC (DMN). Interestingly, response and remission after ECT were associated with a longitudinal increase in connectivity from the posterior DMN to the right CEN after ECT. This suggests that ECT may restore dynamics between the posterior DMN and CEN.

We found dissociable lateralized associations of ECT effectiveness in connections from the PCC to the left and right insula. That is, clinical improvement after ECT was associated with decreased connectivity from the PCC to the left insula, and increased connectivity from the PCC to the right insula. Lateralization in the insula has been associated with aberrant processing of positive emotions [41] and a dissociation between salience detection and cognitive control processes for subsequent behavioral adaptation [42], both phenotypes that are highly disturbed in severe depression. Additionally, lateralized effects in the insula with respect to treatment effectiveness were previously reported for antidepressants [43,44], cognitive behavioral therapy [44], and transcranial magnetic stimulation [45]. Lateralized treatment effects in the insula may thus be an interesting target for future studies on treatments for depression.

Our findings show the added value of effective connectivity analyses using DCM. That is, whereas “regular” functional connectivity analyses did not show any effects, DCM analyses yielded strong evidence for many connectivity correlates. The absence of findings in the mass univariate correlation-based analyses may have been due to a lack of power when correcting for comparisons (i.e., the number of all tested connections, n = 196). Additionally, this contrast in findings may be explained by the different methods used to infer connectivity. Regular correlation-based analysis estimates zero-lag correlations, whereas the data features used by DCM (i.e., the cross-spectral density) is the Fourier transform of the cross-correlation function, which represents the correlation at varying lags. In other words, the data used by DCM is richer than that used by a standard correlation analysis. Additionally, contrary to univariate correlation-based connectivity, DCM uses a neural mass model to infer multivariate directed connections. Also, shrinkage is applied in the PEB model by placing prior probabilities on the regression parameters. For future analyses, DCM analyses with PEB models may rather be compared to multivariate frequentist analyses with shrinkage for a fairer comparison. In this study, we used mass univariate correlation-based analysis, since this is currently the most commonly used method.

Another noticeable finding was that the analyses on ECT effectiveness (i.e., a continuous measure of treatment effect) yielded a much sparser effective connectivity pattern compared to the analyses on

response and remission (i.e., binned effectiveness variables). We performed this dichotomization because it can facilitate the interpretation. Clinically relevant cut-points may increase the clinical relevancy of findings, and ease the translation of research findings to the clinical practice [46]. However, dichotomizing variables that are originally continuous in nature usually has negative statistical effects if used in regression models. It results in a loss of power and effect size, reduced measure reliability and potentially inflated Type 1 errors [46,47]. Also, the loss of information due to dichotomization may increase the probability that the binned variables coincide with unobserved confounds (i.e., unmeasured or unknown clinical, demographic, or treatment characteristics). In contrast to a loss of power, we actually observed more changes in effective connectivity in the dichotomous compared to the continuous analysis. We speculate that this could be the result of a nonlinear but monotonic relationship between changes in effective connectivity and symptoms, and/or the association to other unobserved clinical variables such as comorbidity and medication use. Future studies should assess the sensitivity of neuroimaging analyses to inflated type I errors due to dichotomization.

Multiple limitations should be considered when interpreting these findings. First, these analyses were performed on observational data collected in a cohort study design. Controlled trials are particularly uncommon in ECT-research, due to the difficulty to design a proper control condition. Nevertheless, the current study design did not allow us to separate placebo effects from treatment effects. Second, the sample size of healthy controls (especially the longitudinal sample) was small. This resulted in considerable test-retest variability, reflected by longitudinal changes in effective connections within the healthy control group. Similarly, the number of patients with longitudinal data was considerably smaller compared to the baseline sample. Third, data of different centers were retrospectively pooled. Therefore, specific study characteristics such as treatment indication and data acquisition were not standardized between centers. In the future, studying more homogeneous samples over different sites would be desirable. Additionally, the exact time since last treatment was not available in the database, which is a potential confounder for the relation between treatment effectiveness and effective connectivity. Fourth, data on cognitive outcomes were not available during the time of analysis. Cognitive outcomes are important in studies on ECT, since cognitive adversities are one of its most common side-effects. Finally, we studied effective connectivity in a specific subset of regions within the triple network model. Future studies could focus on including more regions of interest to capture a broader view of ECT effects on effective connectivity.

In conclusion, this multicenter cohort study yielded many effective connectivity parameters of severe depression and its treatment with ECT. This shows the added value of effective connectivity analyses for generating new hypotheses regarding psychopathology and working mechanisms of treatment. This study suggests that the connectivity from the posterior DMN to the bilateral insula is important for the effectiveness of ECT and therefore an interesting target for treatments of severe depression.

CRediT authorship contribution statement

Freek ten Doesschate: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Willem Bruin:** Software, Writing – review & editing. **Peter Zeidman:** Methodology, Writing – review & editing. **Christopher C. Abbott:** Investigation, Writing – review & editing. **Miklos Argyelan:** Investigation, Writing – review & editing. **Annemieke Dols:** Investigation, Writing – review & editing. **Louise Emsell:** Investigation, Writing – review & editing. **Philip F.P. van Eijndhoven:** Investigation, Writing – review & editing. **Eric van Exel:** Investigation, Writing – review & editing. **Peter C.R. Mulders:** Investigation, Writing – review & editing. **Katherine Narr:** Investigation, Writing – review & editing. **Indira Tendolkar:** Investigation, Writing – review & editing. **Didi Rhebergen:** Investigation, Writing – review & editing. **Pascal Sienaert:** Investigation, Writing – review & editing. **Mathieu Vandenbulcke:** Investigation, Writing – review & editing. **Joey Verdijk:** Investigation, Writing – review & editing. **Mike van Verseveld:** Investigation, Writing – review & editing. **Hauke Bartsch:** Resources, Writing – review & editing. **Leif Oltedal:** Resources, Writing – review & editing. **Jeroen A. van Waarde:** Conceptualization, Writing – review & editing, Supervision. **Guido A. van Wingen:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.07.054.

References

[1] James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1789–858.
[2] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. Am J Psychiatr 2006;163(11):1905–17.
[3] Eaton WW, Shao H, Nestadt G, Lee BH, Bienvenu OJ, Zandi P. Population-based study of first onset and chronicity in major depressive disorder. Arch Gen Psychiatr 2008;65(5):513–20.
[4] Heijnen WT, Birkenhäger TK, Wierdsma AI, van den Broek WW. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. J Clin Psychopharmacol 2010;30(5):616–9.
[5] Gbyl K, Videbech P. Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis. Acta Psychiatr Scand 2018;138(3):180–95.
[6] Lorenzetti V, Allen NB, Fornito A, Yücel M. Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J Affect Disord 2009;117(1–2):1–17.
[7] Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. Resting-state functional connectivity in major depressive disorder: a review. Neurosci Biobehav Rev 2015;56:330–44.
[8] Porta-Casteràs D, Cano M, Camprodon JA, Loo C, Palao D, Soriano-Mas C, Cardoner N. A multimetric systematic review of fMRI findings in patients with MDD receiving ECT. Prog Neuro Psychopharmacol Biol Psychiatr 2021;108:110178.
[9] de Aguiar Neto FS, Rosa JLG. Depression biomarkers using non-invasive EEG: a review. Neurosci Biobehav Rev 2019;105:83–93.
[10] Farzan F, Boutros NN, Blumberger DM, Daskalakis ZJ. What does the electroencephalogram tell us about the mechanisms of action of ECT in major depressive disorders? J ECT 2014;30(2):98–106.
[11] Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cognit Sci 2011;15(10):483–506.
[12] Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatr 2015;72(6):603–11.
[13] van de Mortel LA, Bruin WB, Thomas RM, Abbott C, Argyelan M, van Eijndhoven P, Mulders P, Narr KL, Tendolkar I, Verdijk J. Multimodal multi-center analysis of electroconvulsive therapy effects in depression: brainwide gray matter increase without functional changes. Brain Stimul 2022;15(5):1065–72.
[14] Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 1994;2(1-2):56–78.
[15] Razi A, Seghier ML, Zhou Y, McColgan P, Zeidman P, Park H-J, Sporns O, Rees G, Friston KJ. Large-scale DCMs for resting-state fMRI. Netw Neurosci 2017;1(3):222–41.
[16] Kandilarova S, Stoyanov D, Kostianev S, Specht K. Altered resting state effective connectivity of anterior insula in depression. Front Psychiatr 2018;9:83.
[17] Ray D, Bezmaternykh D, Mel'nikov M, Friston KJ, Das M. Altered effective connectivity in sensorimotor cortices is a signature of severity and clinical course in depression. Proc Natl Acad Sci USA 2021;118(40):e2105730118.
[18] Rolls ET, Cheng W, Gilson M, Qiu J, Hu Z, Ruan H, Li Y, Huang C-C, Yang AC, Tsai S-J. Effective connectivity in depression. Biol Psychiatr: Cognit Neurosci Neuroimaging 2018;3(2):187–97.

[19] Schlösser RGM, Wagner G, Koch K, Dahnke R, Reichenbach JR, Sauer H. Fronto-cingulate effective connectivity in major depression: a study with fMRI and dynamic causal modeling. Neuroimage 2008;43(3):645–55.
[20] Wei Q, Ji Y, Bai T, Zu M, Guo Y, Mo Y, Ji G, Wang K, Tian Y. Enhanced cerebro-cerebellar functional connectivity reverses cognitive impairment following electroconvulsive therapy in major depressive disorder. Brain Imag Behav 2021;15(2):798–806.
[21] Wang, Wei Bai, Zhou, Sun, Becker B, Tian Y, Wang K, Kendrick K. Electroconvulsive therapy selectively enhanced feedforward connectivity from fusiform face area to amygdala in major depressive disorder. Soc Cognit Affect Neurosci 2017;12(12):1983–92.
[22] Wang Wang, Huang Jia, Zheng Zhong, Chen G, Huang L, Huang R. Abnormal dynamic functional network connectivity in unmedicated bipolar and major depressive disorders based on the triple-network model. Psychol Med 2020;50(3):465–74.
[23] Oltedal L, Bartsch H, Sørhaug OJE, Kessler U, Abbott C, Dols A, Stek ML, Ersland L, Emsell L, van Eijndhoven P. The Global ECT-MRI Research Collaboration (GEMRIC): establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. Neuroimage: Clinical 2017;14:422–32.
[24] Heo M, Murphy CF, Meyers BS. Relationship between the Hamilton depression rating scale and the montgomery-Åsberg depression rating scale in depressed elderly: a meta-analysis. Am J Geriatr Psychiatr 2007;15(10):899–905.
[25] Pruim RHR, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF. ICA-AROMA: a robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 2015;112:267–77.
[26] Friston KJ, Kahan J, Biswal B, Razi A. A DCM for resting state fMRI. Neuroimage 2014;94:396–407.
[27] Razi A, Kahan J, Rees G, Friston KJ. Construct validation of a DCM for resting state fMRI. Neuroimage 2015;106:1–14.
[28] Bernal-Casas D, Lee HJ, Weitz AJ, Lee JH. Studying brain circuit function with dynamic causal modeling for optogenetic fMRI. Neuron 2017;93(3):522–32.
[29] Raichle ME. The restless brain. Brain Connect 2011;1(1):3–12.
[30] Friston KJ, Litvak V, Oswal A, Razi A, Stephan KE, Van Wijk BCM, Ziegler G, Zeidman P. Bayesian model reduction and empirical Bayes for group (DCM) studies. Neuroimage 2016;128:413–31.
[31] Gelman A, Hill J, Yajima M. Why we (usually) don't have to worry about multiple comparisons. J Res Edu Effect 2012;5(2):189–211.
[32] Friston KJ, Harrison L, Penny W. Dynamic causal modelling. Neuroimage 2003;19(4):1273–302.
[33] Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, Schwerthöffer D, Zimmer C, Förstl H, Bäuml J. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. Front Hum Neurosci 2014;7:930.
[34] Wei Qin, Yan Bi, Liu C, Yao Z, Lu Q. Abnormal dynamic community structure of the salience network in depression. J Magn Reson Imag 2017;45(4):1135–43.
[35] Goulden N, Khusnulina A, Davis NJ, Bracewell RM, Bokde AL, McNulty JP, Mullins PG. The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. Neuroimage 2014;99:180–90.
[36] Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA 2008;105(34):12569–74.
[37] Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 2010;214(5):655–67.
[38] Namkung H, Kim S-H, Sawa A. The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. Trends Neurosci 2017;40(4):200–7.
[39] Avery JA, Drevets WC, Moseman SE, Bodurka J, Barcalow JC, Simmons WK. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. Biol Psychiatr 2014;76(3):258–66.
[40] Wiebking C, Bauer A, De Greck M, Duncan NW, Tempelmann C, Northoff G. Abnormal body perception and neural activity in the insula in depression: an fMRI study of the depressed "material me.". World J Biol Psychiatr 2010;11(3):538–49.
[41] Duerden EG, Arsalidou M, Lee M, Taylor MJ. Lateralization of affective processing in the insula. Neuroimage 2013;78:159–75.
[42] Späti J, Chumbley J, Brakowski J, Dörig N, Grosse Holtforth M, Seifritz E, Spinelli S. Functional lateralization of the anterior insula during feedback processing. Hum Brain Mapp 2014;35(9):4428–39.
[43] Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. Hum Brain Mapp 2008;29(6):683–95.
[44] McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, Craddock RC, Mayberg HS. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatr 2013;70(8):821–9.
[45] Kito S, Hasegawa T, Koga Y. Neuroanatomical correlates of therapeutic efficacy of low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. Psychiatr Clin Neurosci 2011;65(2):175–82.
[46] MacCallum RC, Zhang S, Preacher KJ, Rucker DD. On the practice of dichotomization of quantitative variables. Psychol Methods 2002;7(1):19.
[47] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006;25(1):127–41.
[48] Wang L, Wei Q, Wang C, Xu J, Wang K, Tian Y, Wang J. Altered functional connectivity patterns of insular subregions in major depressive disorder after electroconvulsive therapy. Brain Imag Behav 2020;14(3):753–61.