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Research paper

# Movement, mood and cognition: Preliminary insights into the therapeutic effects of electroconvulsive therapy for depression through a resting-state connectivity analysis

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ABSTRACT

**Background:** Electroconvulsive therapy (ECT) is a highly effective treatment for depression but how it achieves its clinical effects remains unclear.

**Methods:** We set out to study the brain's response to ECT from a large-scale brain-network perspective. Using a voxelwise analysis, we looked at resting-state functional connectivity before and after a course of ECT at the whole-brain and the between- and within-network levels in 17 patients with a depressive episode. Using a group-independent component analysis approach, we focused on four networks known to be affected in depression: the salience network (SN), the default mode network (DMN), the cognitive executive network (CEN), and a subcortical network (SCN). Our clinical measures included mood, cognition, and psychomotor symptoms.

**Results:** We found ECT to have increased the connectivity of the left CEN with the left angular gyrus and left middle frontal gyrus as well as its within-network connectivity. Both the right CEN and the SCN showed increased connectivity with the precuneus and the anterior DMN with the left amygdala. Finally, improvement of psychomotor retardation was positively correlated with an increase of within-posterior DMN connectivity.

**Limitations:** The limitations of our study include its small sample size and the lack of a control dataset to confirm our findings.

**Conclusion:** Our voxelwise data demonstrate that ECT induces a significant increase of connectivity across the whole brain and at the within-network level. Furthermore, we provide the first evidence on the association between an increase of within-posterior DMN connectivity and an improvement of psychomotor retardation, a core symptom of depression.

## 1. Introduction

Electroconvulsive therapy (ECT) is a highly effective and fast-acting treatment for severe depression, with response rates as high as 80% (Kho et al., 2003). Moreover, in addition to its well-known therapeutic effect on mood, ECT has a unique impact on psychomotor symptoms (Belge et al., 2020; Hickie et al., 1996) and cognitive functioning (Semkovska et al., 2010), both core elements of the depressive

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syndrome. However, the mechanism of action by which ECT exerts these effects at the brain level remains largely unknown. Previous research mainly investigated ECT-related changes in brain structures (Mulders et al., 2020; Ota et al., 2015; (Ousdal et al., 2020) Redlich et al., 2016), but the clinical relevance of these changes is unclear as complex functions of the brain such as mood cannot be explained by the function of isolated regions. Far rather, such specific functions rely on the dynamic organization of distant brain regions into functional networks (Bressler et al., 1995; Menon et al., 2011). A large-scale brain-network perspective should then yield new insights into the neurobiological underpinnings of the clinical effects of ECT. Neuroimaging methods such as resting-state fMRI (rs-fMRI) allow the consistent characterization of functional networks that are spatially distributed but show coordinated activity in the absence of a specific task (Biswal et al., 1995). Importantly, this independence of task-based paradigms has the major advantage that findings are reproducible across different populations and study settings. Resting-state analyses are therefore an essential addition to functional imaging techniques in unraveling the neurobiology of neuropsychiatric disorders (Menon et al., 2011). In depression, most resting-state functional connectivity analyses have reported alterations in three core neural networks: the default mode network (DMN), the central executive network (CEN), and the salience network (SN) (Hamilton et al., 2013; Mulders et al., 2015). The DMN is involved in spontaneous and self-referential thought (Buckner et al., 2008), the CEN facilitates the execution of higher-order, cognitively demanding tasks (Corbetta et al., 2002), and the SN is hypothesized to orient attention towards salient information (Seeley et al., 2007).

Intriguingly, previous neuroimaging studies revealed that ECT modifies this altered connectivity in depression, with studies employing a hypothesis-driven seed-based connectivity analysis highlighting post-treatment reversals of the earlier alterations. Abbott et al. (2013) reported a normalization of the decreased connectivity of the right hippocampus to the medial and lateral temporal cortex. A study using the amygdala as a seed region observed a decrease in connectivity to the subgenual anterior cingulate cortex, part of the anterior DMN (Cano et al., 2016). Furthermore, ECT restores the connectivity between prefrontal areas and the dorsal nexus (Perrin et al., 2012), a node of the anterior DMN showing increased depression-associated connectivity with other networks implicated in various aspects of depression (Sheline et al., 2010). Bai and colleagues (2019) demonstrated that the enhanced connectivity between the dorso-medial prefrontal cortex and the precuneus cortex after ECT was positively associated with clinical improvement(Bai et al., 2019). In the same vein, studies utilizing independent component analysis (ICA) revealed ECT to normalize network connectivity between the posterior DMN and the anterior DMN as well as between the posterior DMN and the left CEN (Abbott et al., 2013; Leaver et al., 2016; Perrin et al., 2012; Wang et al., 2018). In contrast to non-responders, ECT seems to resolve decreased DMN coherence localized in the precuneus and angular gyrus in patients with depression who go on to improve clinically (Mulders et al., 2016). Further, an increase in functional connectivity strength between the left angular gyrus, a functional node of the anterior DMN, and the whole brain was observed following ECT (Wei et al., 2018) as well as enhanced intra-network connectivity in the CEN (Wang et al., 2018) While these ECT-induced functional changes appear to be broadly distributed, a recent systematic review concluded that especially the modulation of the superior and middle frontal gyri and the subgenual anterior cingulate cortex are crucial for the mechanisms of action of ECT, thus, from a network perspective highlighting the importance of the CEN and DMN, respectively (Porta- Casteràs et al., 2020).

Yet, how this ECT-induced modulation of connectivity relates to changes in mood, psychomotor symptoms, and cognitive functioning has not been clarified. In an attempt to shed new light on potential underlying mechanisms, we conducted a longitudinal rs-fMRI study in a cohort of adult patients diagnosed with a depressive episode and used an ICA approach to explore changes in connectivity in our networks of interest, i.e. the SN, DMN and CEN. We also included a subcortical network (the SCN) encompassing the basal ganglia, known to be an important part of the brain circuits involved in depression and implicated in the therapeutic effects of ECT (Furman et al., 2011; Gabbay et al., 2013; Menon et al., 2011; Wade et al., 2016), most notably in the improvement of psychomotor symptoms (Belge et al., 2020). First, we aimed to investigate changes in connectivity patterns of these networks across the entire brain. Second, we expanded this whole-brain analysis with aggregate measures of within- and between-network connectivity to identify changes within and between our networks of interest. Our third aim was to investigate whether within-network connectivity changes could be linked to changes in the clinical symptoms of mood, psychomotor functioning and cognition to try and further our understanding of the neurobiological underpinnings and therapeutic effects of ECT for depression.

## 2. Materials and methods

### 2.1. Participants

Patients were recruited at the University Psychiatric Center (UPC) in Duffel, Belgium and needed to fulfil the following inclusion criteria: (1) age over 18 years, (2) a diagnosis of unipolar or bipolar depression as defined by the DSM-IV-TR criteria, (3) a score of $\geq$ 17 on the Hamilton Depression Rating Scale–17 items and (4) an indication for ECT treatment in accordance with the Dutch Guidelines on Electroconvulsive Therapy (van den Broek et al., 2010). Exclusion criteria were drug or alcohol dependence, a primary psychotic disorder as assessed using the MINI interview (Sheehan et al., 1998), being currently enrolled in a study involving a trial drug, and contraindications for MRI (e.g., a pacemaker, claustrophobia, metallic implants). In total, 17 participants were enrolled from whom written informed consent was obtained prior to their inclusion in the study protocol, which was reviewed and approved by both the local ethics board of the UPC Duffel and the central ethics committee of the University Hospital Antwerp. The study was conducted in accordance with the Helsinki declaration.

### 2.2. ECT procedure

ECT was administered twice weekly using a brief-pulse (0.5 ms), constant-current Thymatron IV system (Somatics LLC, Lake Bluff, IL, USA). We routinely used a right unilateral (RUL) electrode position and a bitemporal (BT) positioning when a fast antidepressant effect was needed. Following international recommendations (NICE, 2003), patients were switched to BT if ECT response was inadequate after six treatments. We defined inadequate response as a reduction of less than 25% on the baseline HDRS-17 score (Trajkovic et al., 2011), with the clinical assessment of a trained psychiatrist confirming the lack of response. Stimulus doses were determined by means of the age method for RUL-electrode placement and the half-age estimation method for bilateral electrode positions. Anesthesia was achieved with intravenous administration of etomidate (0.15 mg/kg) or with propofol (1 mg/kg) in cases where etomidate was not (well) tolerated. We used succinylcholine (0.5 mg/kg) as a muscle relaxant. The ECT regimen was continued until the moment the patient was in remission (HDRS-17 $\leq$ 7), showed no further improvement during the last three sessions, or reported intolerable side effects.

### 2.3. Clinical measures

All clinical assessments were conducted within one week before (T1) the start of the first ECT session and within one week (T2) after conclusion of the ECT course.

### 2.4. Mood

Mood was assessed using the Hamilton Rating Scale for Depression–17 items (HDRS-17) (Trajkovic et al., 2011). Treatment response was defined as a reduction of 50% or more on the HDRS-17. Remission was defined as a HDRS-17 score $\leq 7$.

### 2.5. Cognition

Global cognitive performance was gauged using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005).

### 2.6. Psychomotor symptoms

Psychomotor performance was evaluated by means of the CORE rating scale, a clinician-administered inventory used to measure observable impairments in psychomotor functioning (Rhebergen et al., 2012). During the assessment, 18 discernible clinical features related to psychomotor functioning are scored on a 4-point severity scale ranging from 0 (Absence of the symptom assessed) to 3 (Severe manifestation of the symptom). A decrease in CORE scores implies an improvement of the psychomotor symptoms assessed.

### 2.7. MRI acquisition and processing

#### 2.7.1. Rs-fMRI data acquisition

Images were consistently obtained within the week before a participant's first ECT session (T1) and within one week (T2) after completion of the acute course by means of a 3T Siemens Magnetom Prisma MRI scanner (Erlangen, Germany) with a 32-channel head coil. T2*-weighted EPI BOLD-fMRI images were acquired for the resting-state scans, using a multi-band 6 protocol with an interleaved slice acquisition sequence (number of slices = 66, TR = 1000 ms, TE = 34 ms, flip angle = 60°, voxel size = 2.0 Å~ 2.0 Å~ 2.0 mm, slice gap = 0 mm, FOV = 210 mm). High-resolution structural images were acquired using a three-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo sequence (MPRAGE) with the following acquisition parameters: TI 900 [ms], TR 2300 [ms], TE 2.98 [ms], flip angle 9 [deg], voxel-size 1.0 Å~ 1.0 Å~ 1.0 [mm]. Each scan consisted of 200 volumes.

#### 2.7.2. Rs-fMRI preprocessing

Preprocessing and statistical analyses were performed on all pre- and post-ECT resting-state scans collected using FSL 6.0.3 (FMRIB, Oxford, UK). The scans were preprocessed using the FMRI Expert Analysis Tool (FEAT) (Jenkinson et al., 2012; Beckmann et al., 2012). To allow for T2* equilibration effects, the first five images of each resting-state scan were discarded (resulting in 195 volumes). Furthermore, the preprocessing steps included brain extraction, motion correction, bias field correction, high-pass temporal filtering with a cut-off of 100 s, spatial smoothing with a 4-mm full width at half maximum (FWHM) Gaussian kernel, registration of functional images to high-resolution T1 using boundary-based registration and nonlinear registration to standard space (MNI152). The final voxel size for group analysis was 2 mm isotropic. We used ICA-based Advanced Removal of Motion Artefacts (ICA-AROMA) for further single-subject denoising (Jenkinson et al., 2012; Beckmann et al., 2012).

#### 2.7.3. Rs-fMRI analyses

ECT-induced functional connectivity changes in the DMN, SN, CEN, and SCN were addressed at three levels: (1) voxelwise across the whole brain, (2) between-network connectivity and (3) within-network connectivity.

(1) Voxelwise across the whole brain

The networks of interest were identified using group ICA (Beckmann et al., 2005). We visually identified our networks and through cross correlation of the output of the group ICA (scans 1 and 2 combined) with networks from Smith's 20-dimensional ICA, rs-FMRI components template (https://www.fmrib.ox.ac.uk/datasets/brainmap±rsns/). Dual regression was used to investigate the connectivity changes of the various networks voxelwise across the whole brain. Inference testing was implemented using permutation testing via randomize (5000 permutations) (Winkler et al., 2014). The test results were considered significant using an FDR corrected p-value of 0.05 and a minimum cluster size of 20 voxels.

(2) Between-network connectivity

To analyze between-network connectivity, the time courses resulting from dual regression were fed into FSLNets (v0.6) for network modeling (Smith et al., 2013). Of the 20 networks, 14 were discarded and the remaining six networks (the anterior DMN, posterior DMN, left CEN, right CEN, SCN, and SN) were used to create a network x network correlation matrix, with each matrix element representing the correlation strength between the corresponding pair of networks. To obtain a better estimate of the direct connections between networks, we used partial correlation coefficients that were converted from Pearson correlation r-values into z-statistics with Fisher's transformation (Smith et al., 2013; Suri et al., 2017). The six networks were reordered according to a hierarchical clustering of the group-average full correlation network matrix using Ward's method implemented in MATLAB® to generate the functional connectome.

(3) Within-network connectivity

To determine within-network connectivity, thresholded spatial network maps ($Z \geq 3$) were used as masks to extract the mean within-network connectivity strength in both resting-state scans (van Oort et al., 2020). This results in one value per subject and network, representing an aggregate measure of mean within-network connectivity. The effect of ECT on within-network connectivity was examined with a paired comparison between the connectivity strength in the resting-state scan before and the resting-state scan after ECT using a paired *t*-test (with normal distribution being tested using the Shapiro-Wilk procedure).

Finally, we performed exploratory Pearson correlational analyses between significant ECT-induced changes of connectivity within the networks (T2-T1) and significant changes in the clinical measures (T2-T1) (HDRS-17, MoCA, CORE (retardation and agitation)). Bonferroni correction was carried out for the number of networks analyzed, resulting in a final significance threshold of $p<0.008$. Age was included as a nuisance regressor to assess its possible influence on those results reaching significance.

## 3. Results

### 3.1. Participants

Table 1 summarizes the demographics, clinical characteristics, and ECT treatment information of the study population.

### 3.2. Clinical measurements

The pre- and post-treatment clinical outcomes can be found in Table 2. ECT had a significant effect on depressive symptoms, as is demonstrated by the significant drop in HDRS-17 scores ($p < 0.0001$). Global cognitive performance, as measured with the MoCA, had declined following ECT but not significantly so ($p = 0.25$). A significant interaction was not observed between the change in HDRS-17 scores and the change of global cognitive performance ($p = 0.53$). Both psychomotor agitation ($p < 0.003$) and retardation ($p < 0.004$) had improved significantly following ECT, as is reflected by the significant reduction in the respective CORE subscale scores.

**Table 1**
Demographics, clinical characteristics, and ECT protocol information for all participants.

| Variable | $n = 17$ |
|---|---|
| **Demographic Information** | |
| Age, mean years (SD) | 57.8 (11.0) |
| Gender (M/F) | 3/14 |
| **Clinical Characteristics** | |
| Current episode duration, mean months (SD) | 15.2 (5.9) |
| Unipolar/bipolar depression | 14/3 |
| **ECT Protocol** | |
| Unilateral/bilateral lead placement | 14/3 |
| Number of ECT Index sessions, mean (SD) | 11 (5.93) |
| Number of ECT Index sessions, range | 4–25 |
| Number of antidepressants at the time of treatment (patients) | 0 (0)<br>1 (8)<br>2 (2)<br>3 (2)<br>4 (1) |
| Respondersa, n (%) | 15 (88.3%) |
| Remissionb, n (%) | 12 (71%) |
| **Clinical testings/MRI** | |
| Days before the first ECT, mean (SD) | 3.64 (1.77) |
| Days after the last ECT, mean (SD) | 3.58 (1.46) |

Abbreviations: ECT=electroconvulsive therapy; F=female; M=male; SD=standard deviation; HDRS17=Hamilton Depression Rating Scale 17 Items.
[a]Response was defined as a 50% or larger baseline to end-of-treatment reduction in HDRS17 scores.
[b]Remission was defined as an HDRS17 score≤.7

**Table 2**
Clinical assessments.

| | Before ECT (mean; SD) | After ECT (mean; SD) | Δ (mean; SD) | P-value (t) |
|---|---|---|---|---|
| **HDRS17** | 23.71; 6.97 | 7.65; 5.11 | - 16.06; 9.54 | **<0.0001** (−6.94) |
| **MoCA** | 24.82; 3.84 | 23.94; 4.32 | - 0.88; 3.02 | 0.25 (−1.2) |
| **CORE retardation** | 4.53; 5.1 | 0.24; 0.44 | - 4.29; 5.01 | **<0.003** (-3.53) |
| **CORE agitation** | 1.94; 2.08 | 0.06; 0.24 | - 1.88; 2.06 | **<0.004** (-3.77) |

Abbreviations: ECT=electroconvulsive therapy; HDRS17=Hamilton Depression Rating Scale 17 Items; MoCA=Montreal Cognitive Assessment; SD=standard deviation; Δ=difference scores (after ECT – before ECT).

### 3.3. Rs-fMRI

#### 3.3.1. Independent component analysis

We used ICA to decompose our data into 20 independent components that correspond to well-known large-scale networks as previously described in the literature (Smith et al., 2009). Looking at the designated networks (the DMN, CEN, SN, and the SCN; see Fig. 1.), we identified two ICAs that comprised the DMN, i.e., the anterior and posterior DMN, and two CENs, i.e., the left and right CEN. The anterior DMN included the ventromedial prefrontal cortex, while the posterior DMN involved the posterior cingulate cortex and precuneus. Both CENs included the dorsolateral prefrontal cortex and posterior parietal cortex. The SN comprised the bilateral anterior insula and dorsal anterior cingulate cortex and the SCN the ventral anterior cingulate cortex, the bilateral thalamus, pallidum, putamen, and caudate nucleus. The selected networks included all areas that are typically considered core regions in these networks ( Smith et al., 2009).

#### 3.3.2. Whole-brain analysis

The results of the whole-brain analyses of our networks of interest are represented in Fig. 2 and Table 3. Importantly, after FDR correction, only increases in connectivity remained significant. After ECT, an increased resting-state functional connectivity was observed between the anterior DMN and the left amygdala and between the left CEN-left angular gyrus and between the right CEN-right precuneus cortex. Furthermore, post-ECT, the connectivity between the left CEN and the left middle frontal gyrus showed an increase, as was the case between the CEN and the cerebellum, between the left CEN - right crus I and the right CEN and left lobules I-IV, respectively. Finally, the SCN showed an increase of connectivity with the left precuneus and the left superior frontal gyrus.

#### 3.3.3. Within-network connectivity

Table 4 displays the within-network connectivity results. Whilst all networks showed a tendency towards increased within-network connectivity after ECT, this was significant for the left CEN only.

#### 3.3.4. Between-network connectivity

No significant changes in between-network connectivity following ECT were observed (see Fig. 3).

#### 3.3.5. Exploratory correlations between ECT-induced changes in within-network connectivity and the clinical outcomes

See Table 5 and Fig. 4 for the results of the correlational analyses. Post-ECT change in within-posterior DMN connectivity was negatively correlated with the change in psychomotor retardation, indicating that a more marked increase of within-posterior DMN connectivity is associated with a stronger reduction in psychomotor retardation scores. This correlation was also found for the anterior DMN, but it failed to remain significant following Bonferroni correction. We further observed moderate negative correlations between the change in HDRS-17 scores and within-posterior/anterior DMN connectivity, and between the change in MoCA scores and within-left-CEN connectivity, but none of these correlations were significant.

The nuisance regressor (age) did not influence any of the results reaching statistical significance.

## 4. Discussion

Our study demonstrates an increase of connectivity between networks and certain brain regions and within-network connectivity in patients having received a course of ECT for depression. Our main findings are three-fold. First, the increase in left-CEN within-network connectivity was most prominent. Beyond this significant change, ECT also intensified the connectivity between the left CEN and the left angular gyrus. In addition, we observed an increase in connectivity between the left CEN and the left middle frontal gyrus. Secondly, both the right CEN and the SCN showed heightened connectivity with the precuneus cortex. Furthermore, improvements of psychomotor retardation were positively correlated with an amplified within-posterior DMN connectivity. Thirdly, the anterior DMN showed an augmented connectivity with the left amygdala.

Advances in network-based research in system-level neurosciences have highlighted depression as a syndrome that is caused by the distributed effects resulting from anomalies in the interactions among various networks of the brain (Hamilton et al., 2013). It has been proposed that the generalized epileptic seizure induced by ECT may contribute to the modulation of the aberrant network connectivity associated with depression (Wei et al., 2018). During this seizure, the neurons in the brain are activated simultaneously and synchronously, which would then boost the functional connectivity among brain regions (Grasse et al., 2013; Lisanby et al., 2007; Wei et al., 2018). This assumption is supported by our findings of an increase in connectivity between networks and certain brain regions and the increase of left-CEN within-network connectivity.

A vast body of research has reported alterations of the CEN in depression (Alexopoulos et al., 2012), the network encompassing the dorsolateral prefrontal cortex and the posterior parietal cortex. Recent studies report a consistent decrease in connectivity of the dorsolateral

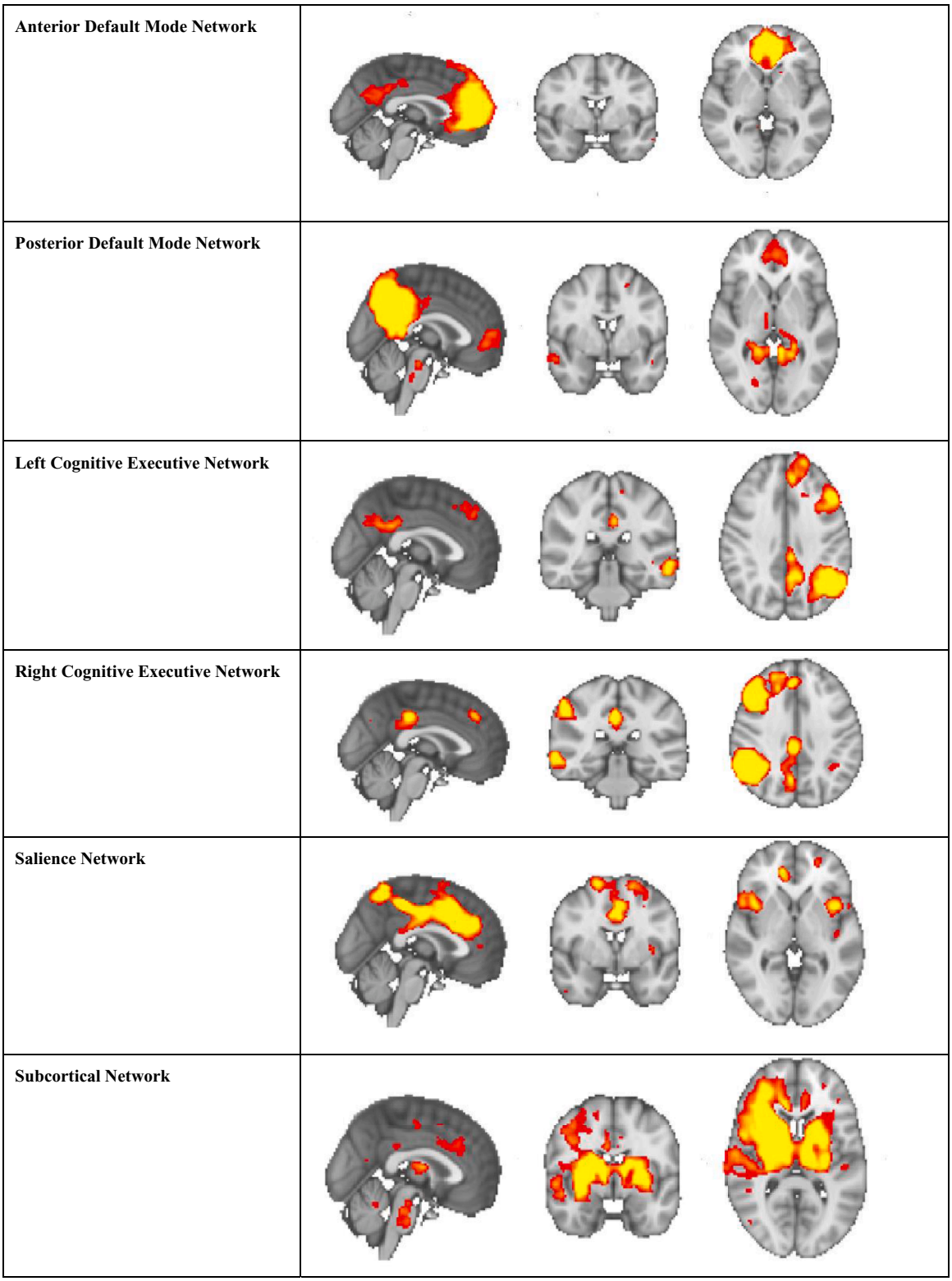



**Fig. 1.** Networks of interest. Networks of interest identified with group-independent component analysis (ICA), i.e. the anterior and posterior Default Mode Network (DMN), the left and right Cognitive Executive Network (CEN), the Salience Network (SN), and the Subcortical Network (SCN). These network maps are group maps that combine the individual template maps of all participants before and after electroconvulsive therapy. Left, and right are switched in the caption.

prefrontal cortex with other regions of the CEN in depression (Alexopoulos et al., 2012; Liston et al., 2014; Ye et al., 2012). Hypothetically, this could reflect an attenuated top-down cognitive control from the dorsolateral prefrontal cortex of limbic hyperactivity, instigating pervasive negative thoughts and feelings of sadness, guilt, and worthlessness (Mayberg et al., 1997; Northoff et al., 2011; Rive et al., 2013). Interestingly, we observed both an increase of left-CEN within-network connectivity, as did Wang et al. (2018), and an augmented connectivity between the left CEN and the left-middle frontal gyrus. Of note from a functional point of view, this anatomical region is mainly

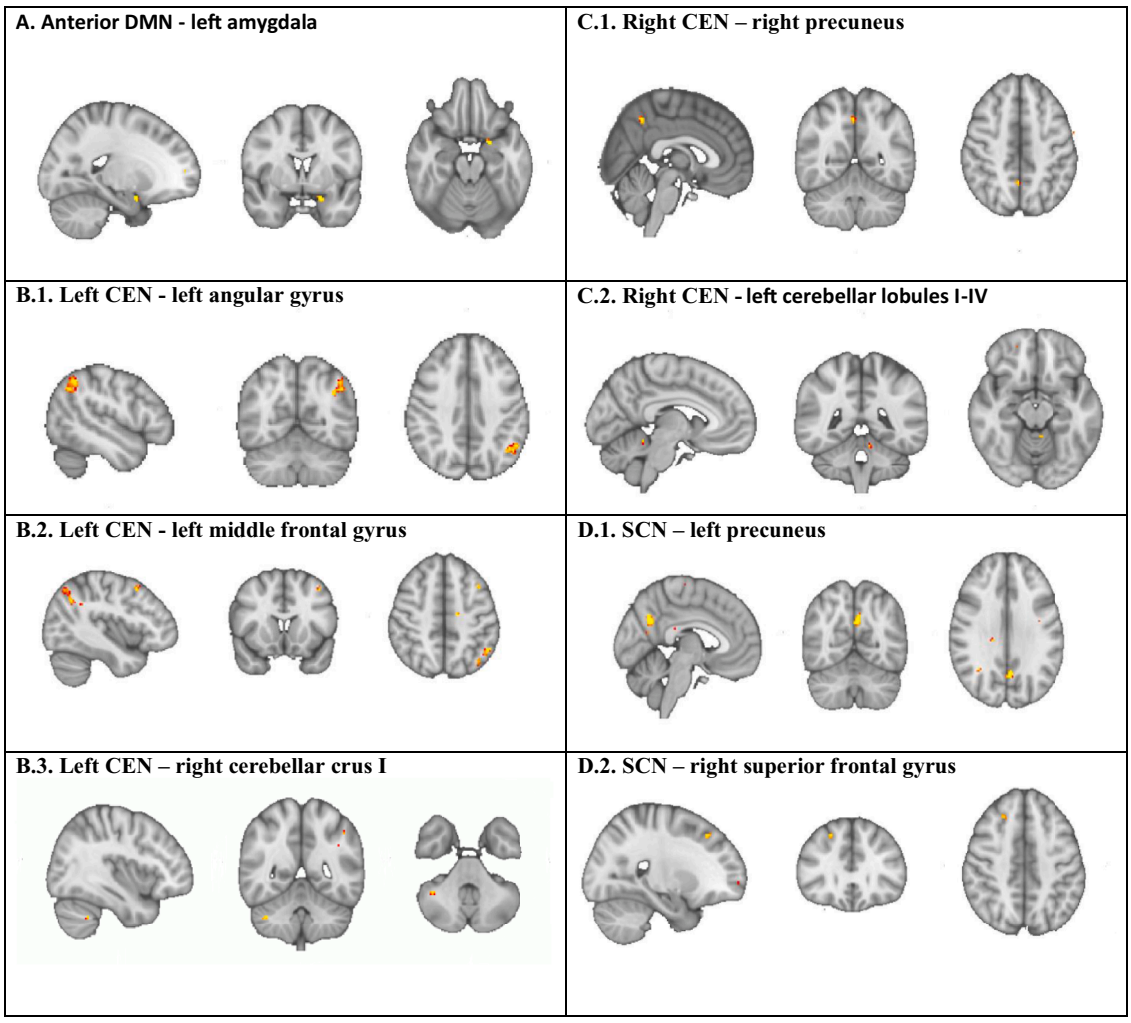



**Fig. 2.** Whole-brain analyses of the networks of interest. Figures A-D display changes in whole-brain connectivity of the selected networks of following electroconvulsive therapy. **A.** There is an increased functional connectivity of the anterior default mode network (DMN) with the left amygdala. **B.1.** Increased connectivity of the left cognitive executive network (CEN) with the left angular gyrus, **B.2.** left middle frontal gyrus and **B.3.** right cerebellar Crus I region. **C.1.** Increased connectivity of the right CEN with the right precuneus and **C.2.** left cerebellar lobules I-IV **D.1.** Increased connectivity of the SCN with the left precuneus and **D.2** with the superior frontal gyrus. Left, and right are switched in the caption.

**Table 3**
ECT-induced functional connectivity changes for the whole-brain analyses.

| Networks | Effect | Brain areas | Hemisphere | Cluster (voxels) | Max. Z (X, Y, Z) | Max. Z | p-Value |
|---|---|---|---|---|---|---|---|
| **Anterior DMN** | | | | | | | |
| | ↑ | amygdala | left | 22 | 55, 64, 26 | 6.67 | <0.0001 |
| **Posterior DMN** | | | | | | | |
| | – | – | – | – | – | | – |
| **Left CEN** | | | | | | | |
| | ↑ | Angular gyrus | Left | 411 | 70, 36, 60 | 5.54 | 0.0005 |
| | ↑ | Middle frontal gyrus | left | 34 | 65, 70, 60 | 5.01 | 0.003 |
| | ↑ | Cerebellum, Crus I | Right | 20 | 26, 38, 17 | 5.33 | 0.005 |
| **Right CEN** | | | | | | | |
| | ↑ | Precuneus cortex | right | 27 | 44, 36, 59 | 5.5 | 0.001 |
| | ↑ | Cerebellum, I-IV | left | 24 | 48, 40, 29 | 4.97 | <0.01 |
| **SN** | | | | | | | |
| | – | – | – | – | – | | – |
| **SCN** | | | | | | | |
| | ↑ | Precuneus cortex | left | 95 | 47, 32, 51 | 7.15 | <0.00001 |
| | ↑ | Superior frontal gyrus | right | 29 | 33, 77, 59 | 5.09 | 0.004 |

Abbreviations: ECT=electroconvulsive therapy; DMN=Default Mode Network; CEN=Cognitive Executive Network; SN=Salience Network; SCN; Subcortical Network.

constituted by the dorsolateral prefrontal cortex, the target area for repetitive magnetic stimulation. Post-ECT, we found that the connectivity between the left CEN and the left angular gyrus had, moreover, intensified, thus replicating and extending the findings of Wei et al. (2018) who, by determining the functional connectivity strength, demonstrated an increase in functional connectivity strength between

**Table 4**
ECT-induced functional connectivity changes for the within-network analyses.

| | Before ECT (mean; SD) | After ECT (mean; SD) | Δ (mean; SD) | p-value (t) |
|---|---|---|---|---|
| **Anterior DMN** | 4.39; 2.27 | 4.97; 2.86 | 0.58; 2.47 | 0.36 (0.95) |
| **Posterior DMN** | 3.32; 2.75 | 4.83; 2.46 | 1.51; 2.76 | 0.11 (1.87) |
| **Left CEN** | 4.16; 1.85 | 6.13; 1.49 | 1.97; 1.52 | **<0.0001 (5.36)** |
| **Right CEN** | 5.68; 2.62 | 7.00; 2.50 | 1.32; 3.39 | 0.13 (1.60) |
| **SN** | 4.28; 1.95 | 4.93; 2.09 | 0.65; 1.75 | 0.63 (0.50) |
| **SCN** | 1.83; 1.68 | 2.28; 2.03 | 0.45; 2.36 | 0.44 (0.78) |

Abbreviations: ECT=electroconvulsive therapy; DMN=Default Mode Network; CEN=Cognitive Executive Network; SN=Salience Network; SCN; Subcortical Network; SD=standard deviation; Δ=difference scores (after ECT– before ECT).

the left angular gyrus and the whole brain following ECT (Wei et al., 2018). The angular gyrus processes information by connecting distinct, functionally specialized regions related to emotion regulation (Achard et al., 2006). Relevantly, a whole-brain functional connectome study confirmed a decreased connectivity of the left angular gyrus in depression (Lai et al., 2017).

Notably, the angular gyrus is a functional node of the posterior DMN, a subnetwork of the DMN that shares similar temporal dynamics with the anterior DMN but has a divergent function, playing important roles in both self-consciousness and self-reflective processes through its relation to the hippocampal formation (Andrews-Hanna et al., 2014; Cavanna et al., 2006; Leech et al., 2014; Sheline et al., 2010). The importance of the posterior DMN and its functional nodes in the neurobiological mechanisms of ECT is further emphasized by our findings. As a matter of fact, we revealed an increased connectivity of both the right CEN and SCN with the precuneus cortex, a core hub of the posterior DMN that is implicated in a myriad of cognitive functions through specific cortical connections (Cavanna, et al., 2006). In depression, a generalized reduced connectivity of the precuneus with other large-scale networks has been observed (Peng et al., 2015) and linked to an increase in a depression-related overgeneralization of memories (Zhu et al., 2012). Abbot et al. (2013) specifically found decreased connectivity between the CEN and the posterior DMN in depressive patients and our observation of its normalization following ECT is consistent with their findings. This reduced CEN-posterior DMN connectivity may then account for the difficulty depressed patients experience in switching from a "default-state", in which the DMN is dominant and attention focused on internal mental events, to an "executive state", in which the CEN is dominant and attention is directed towards external stimuli (Hamilton et al., 2011), resulting in excessive ruminations and other self-referential activities.

Interestingly, also the SCN, encompassing the basal ganglia, showed an increased connectivity with the precuneus cortex following ECT. Attenuated cortico-striatal connectivity has been observed in depressed patients and is suggested to underlie various cognitive deficits (Furman et al., 2011). Cognitive flexibility in particular seems to depend on the connectivity between the precuneus and the ventral striatum (Vatansever et al., 2016). The role of the basal ganglia in cognitive circuits is furthermore highlighted by the augmented connectivity between the SCN and the left superior frontal gyrus, a loop that is deeply involved in cognitive processing (Baier et al., 2010; McNab et al., 2008). Importantly, apathy, a core symptom of depression, may affect the functional connectivity between the DLPFC and the basal ganglia during cognitive processes, resulting in a poorer performance on tests tapping into working memory and attention (Fazio et al., 2016). Together, our findings suggest that the therapeutic properties of ECT on mood symptoms may rely on changes in functional networks that lead to a reinforced top-down cognitive control of limbic hyperactivity and an improved ability to switch from a default to an executive state, whereas its effects on cognitive symptoms might be mediated by dynamic interactions between the basal ganglia and cortical nodes of both the posterior DMN and CEN.

To our knowledge, our post-ECT analyses are the first to reveal an

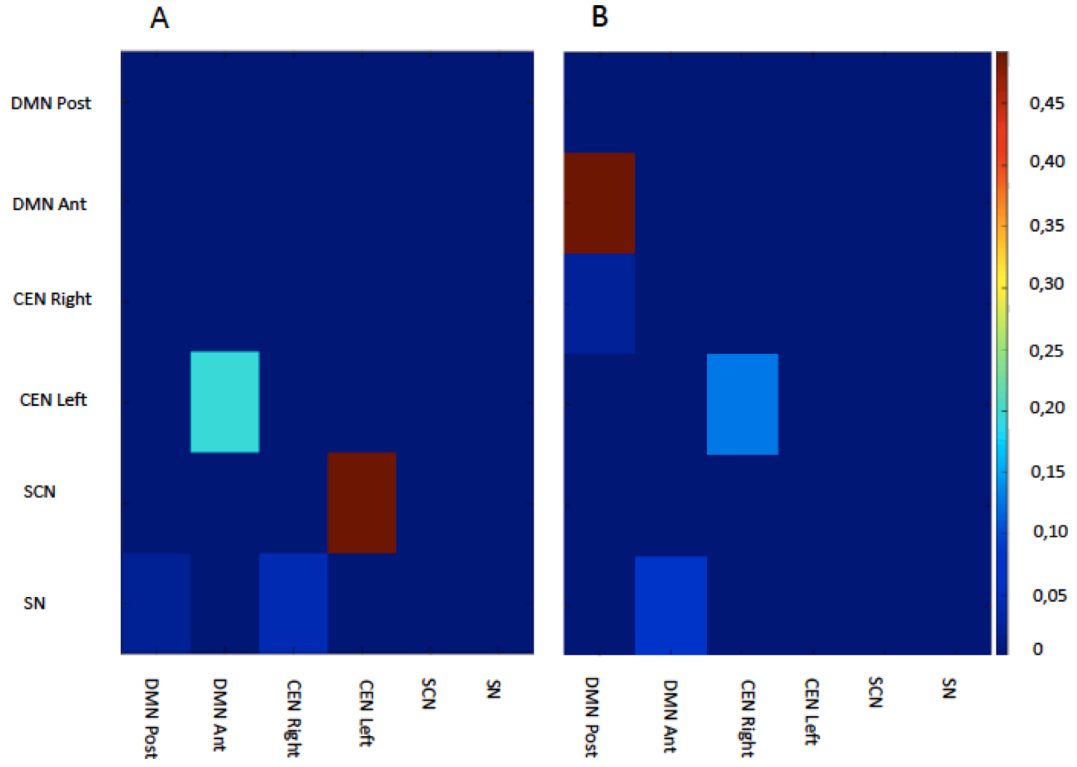



**Fig. 3.** Graphical representation of between-network connectivity changes. Panel A represents changes tending towards a decreased connectivity after ECT, Panel B represents changes tending towards an increased connectivity after ECT. The color legend represents 1-P values. None of the changes were significant.

**Table 5**
Correlational analyses of ECT-induced changes in clinical measures and within-network functional connectivity.

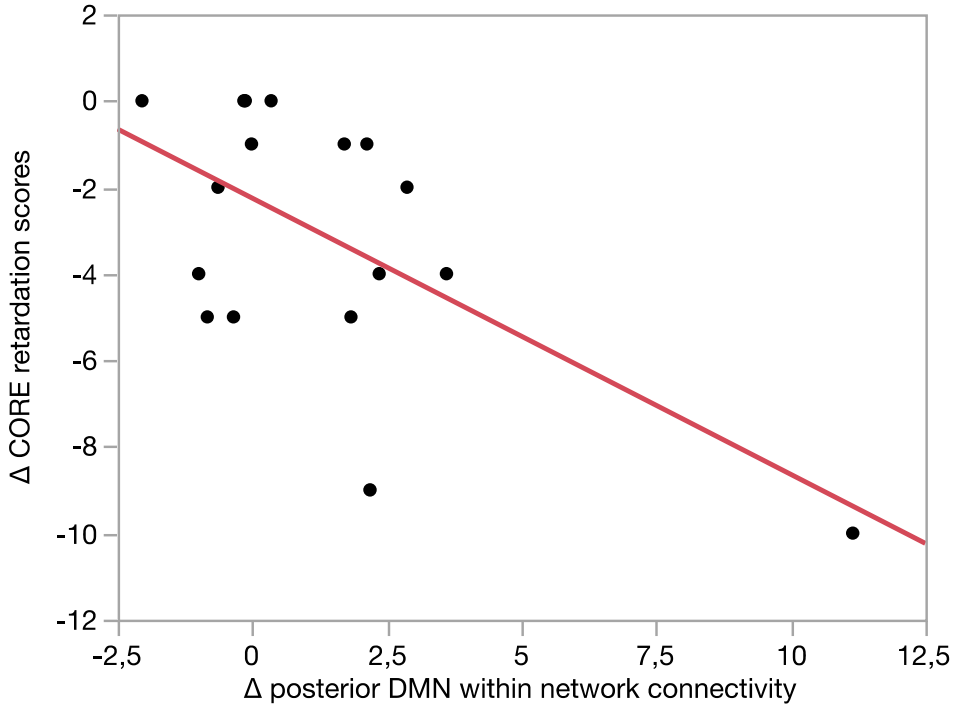
| | Δ-HDRS17 | Δ-MoCA | Δ- CORE agitation | Δ- CORE retardation |
|---|---|---|---|---|
| **Δ- within anterior DMN FC** | r=-0.43 | r = 0.12 | r = 0.13 | r=-0.56 |
| **Δ- within posterior DMN FC** | r=-0.44 | r = 0.05 | r = 0.17 | r=-0.62, **p = 0.0076** |
| **Δ- within left CEN FC** | r=-0.31 | r=-0.39 | r = 0.01 | r=-0.35 |
| **Δ- within right CEN FC** | r = 0.06 | r=-0.25 | r = 0.09 | r = 0.12 |
| **Δ- within SN FC** | r=-0.21 | r = 0.19 | r = 0.19 | r=-0.28 |
| **Δ- within SCN FC** | r = 0.25 | r=-0.18 | r = 0.09 | r = 0.09 |

Abbreviations: ECT=electroconvulsive therapy; DMN=Default Mode Network; CEN=Cognitive Executive Network; SN=Salience Network; SCN; Subcortical Network; Δ=difference scores (after ECT – before ECT); HDRS17=Hamilton Depression Rating Scale 17 Items; MoCA=Montreal Cognitive Assessment; FC=Functional Connectivity.

association between an intensified posterior within-DMN connectivity and improved psychomotor retardation. This novel finding extends previous work of our research team (Belge et al., 2020) and provides new insight into the neurobiology of psychomotor retardation, proposed to be a core symptom of depression with a limited response to other antidepressant therapies (Buyukdura et al., 2011). It supports preliminary evidence brought forward by Treserras et al. (2009) who suggested that, in addition to the cortical motor areas and basal ganglia, the DMN plays a role in the preparation of movement. In fact, through complex dynamic interactions with the motor networks, the DMN seems to modulate motor processing by influencing the state of motor readiness and assisting the supplementary motor area during the coordination of motor behavior (Bazan et al., 2015). Further, the precuneus is believed to subserve the ability to shift attention between different locations in space necessary for bimanual modes of coordinated behavior (Wenderoth et al., 2005). Moreover, as a direct measure of psychomotor speed, reaction times recorded for different sensory-motor tasks seem to correlate with precuneus activation in that participants show more prominent reductions in reaction times with a more prominent activation of the precuneus (Oishi et al., 2005). Fascinatingly, the notion that the DMN influences psychomotor behavior is consistent with abundant evidence of the complex intertwinement between motor processes and higher cognitive functions (Haggard, 1993).

Also the increased connectivity of the anterior DMN with the left amygdala is worth mentioning. In contrast to the posterior DMN, the anterior DMN is more related to self-referential processing and emotion regulation through its strong connections with the amygdala (Andrews-Hanna et al., 2014; Cavanna et al., 2006; Leech et al., 2014). Several papers indicate an altered connectivity between the amygdala and the anterior DMN (Mulders et al., 2015), while amygdala hyperactivity, especially in response to negative stimuli, is a common finding in patients with depression (Price et al., 2010). These alterations are thought to underlie the negativity bias in depression (Price et al., 2010). It is tempting to propose that mentioned augmented connectivity following ECT may serve as a vehicle for the improvement of emotion regulation.

Finally, we observed that the connectivity between the CEN and the cerebellum was enhanced. Various reports indicate an altered neural response in the cerebellum and a reduced cerebellar volume during a depressed state (Konarski et al., 2005). Of note here is that, beyond motor functions, the cerebellum also subserves emotion processing and various cognitive functions through connections with the limbic system and the prefrontal cortex (Depping et al., 2018). Crucially, reduced cerebellar coupling with the CEN in adults with depression has been




DMN = Default Mode Network; Δ = difference scores (after ECT – before ECT)

**Fig. 4.** The relationship between psychomotor retardation and within-posterior DMN connectivity
DMN=Default Mode Network; Δ=difference scores (after ECT – before ECT).

documented to be associated with deficits in cognitive control (Liu et al., 2012). Future research could benefit from looking at this specific network connectivity to enlighten the complex underpinnings of the cognitive effects of ECT.

As to the strengths of our study, we like to mention its longitudinal design, our use of state-of-the-art ICA covering all major neural networks, and the fact that we explored both within- and between-network connectivity in relation to three core clinical symptom domains assessed with validated measures. The limitations of our study include its small sample size, with unknown generalization to larger populations of patients with depression, and the lack of a control dataset to confirm our findings. Collaborative efforts such as the Global ECT-MRI Research Collaboration (GEMRIC) may provide data to confirm and improve our hypotheses. The intervals between testings and the beginning and end of the ECT course are somewhat longer in comparison to similar studies and our findings therefore do not as such reflect the patients' clinical and neurobiological status immediately before and after ECT. On the other hand, immediate testing may reflect the acute postictal effects of ECT more than its antidepressant effects. Further, as our sample consisted of a combination of 14 unipolar patients and 3 bipolar patients, this could likely have attenuated the treatment effects. It should also be noted that the networks we mapped are representative of the patient group examined and thus foremost suitable for the longitudinal assessment of network changes in this group. Finally, when we consider the observed correlation without the patient displaying the most severe signs of psychomotor retardation, the relationship was no longer significant ($r = -3.0$, $p = 0.2$). Even though his psychomotor retardation score was somewhat high (CORE =11), it still is a realistic score that was obtained by a trained clinician, with similar and higher values having been reported in other studies (Van Diermen et al., 2019). Moreover, the within-network changes recorded for this patient are consistent with those of the other patients in our cohort. Taking into account the relatively small sample size, we did not consider it opportune to exclude this patient as an outlier. It remains, nevertheless, important that our findings are replicated in future studies that also include depressed patients with relatively severe psychomotor retardation.

In summary, ours is the first study to combine an ensemble of clinical measures with a data-driven rs-FMRI analysis to inform the neurobiological underpinnings of ECT. Our findings parallel growing evidence on well-known resting-state connectivity alterations in depression implicated in both emotion processing and cognitive control and provide insight into the neurobiological mechanisms of ECT. Moreover, the prominence of the observed changes in connectivity between the CEN and certain brain regions and of CEN within-network connectivity solidifies the reported relevance of the CEN in depression. Finally, we found preliminary evidence of the implication of the DMN in the psychomotor effects of ECT.

## CRediT authorship contribution statement

**Jan-Baptist Belge:** Conceptualization, Methodology, Formal analysis, Software, Writing – original draft. **Peter C.R. Mulders:** Methodology, Formal analysis, Software, Writing – review & editing. **Jasper Van Oort:** Formal analysis, Writing – review & editing. **Linda Van Diermen:** Data curtion, Writing – review & editing. **Ervin Poljac:** Writing – review & editing. **Bernard Sabbe:** Writing – review & editing. **Philippe de Timary:** Writing – review & editing. **Eric Constant:** Writing – review & editing. **Pascal Sienaert:** Writing – review & editing. **Didier Schrijvers:** Funding acquisition, Supervision, Writing – review & editing. **Philip van Eijndhoven:** Methodology, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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