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Research paper

Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy

Peter C.R. Mulders [a,b,*], Philip F.P. van Eijndhoven [a,b], Joris Pluijmen [a], Aart H. Schene [a,b], Indira Tendolkar [a,b,c], Christian F. Beckmann [b]

[a] Department of Psychiatry, Radboud University Medical Center, Huispost 961, Postbus 9101, 6500 HB Nijmegen, The Netherlands
[b] Donders Institute for Brain, Cognition and Behavior, Centre for Neuroscience, P.O. Box 9010, 6500 GL Nijmegen, The Netherlands
[c] Department of Psychiatry and Psychotherapy, University Hospital Essen, Virchowstraße 174, 45147 Essen, Germany

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ABSTRACT

Background: Functional connectivity in the "default mode network" (DMN) is changed in depression, and evidence suggests depression also affects the DMN's spatial topography and might cause a dissociation between its anterior and posterior regions. As antidepressive treatment affects anterior and posterior regions of the network differently, how depression and treatment change DMN-organization is crucial for understanding their mechanisms. We present a novel way of assessing the coherence of a network's regions to the network as a whole, and apply this to investigate treatment-resistant depression and the effects of electroconvulsive therapy (ECT).
Methods: Resting-state functional MRI was collected from 16 patients with treatment-resistant depression before and after ECT and 16 healthy controls matched for age and sex. For each subject, the mean time series of the DMN was used as a regressor for each voxel within the DMN, creating a map of "network coherence" (NC). The obtained maps were compared across groups using permutation testing.
Results: NC was significantly decreased in depressed subjects in the precuneus and the angular gyrus. With ECT the NC normalized in responders (n=8), but not in non-responders (n=8).
Conclusions: We present a novel method of investigating within-network coherence and apply this to show that in depression, a large area of the DMN shows a decrease in coherence to the network as a whole. Although tentative due to the small sample size, we find that this effect is not present after ECT in those improving clinically, but persists in patients not responding to ECT.

1. Introduction

Major depressive disorder (MDD) is a common and disabling psychiatric disorder. For patients not responding to regular treatment (treatment-resistant) electroconvulsive therapy (ECT) is the most potent treatment option to relieve depression (Husain et al., 2004; Whiteford et al., 2013). The pathophysiology of MDD is far from understood, but recent evidence indicates a key role for large-scale networks, and specifically the default mode network (DMN). The DMN is also promising as a target for the antidepressant effects of ECT (Abbott et al., 2013; Beall et al., 2012; Drevets et al., 2008; Kaiser et al., 2015; Mulders et al., 2015; Perrin et al., 2012).

The DMN consists of an anterior and a posterior part with the medial prefrontal cortex and the posterior cingulate cortex/precuneus as its "core" midline regions and several associated areas, such as the inferior parietal lobules and the lateral temporal cortex. Functionally the DMN is related to self-referential processing including self-generated thought, awareness and memory processing, drawing upon its connections with the extended hippocampal formation (Andrews-Hanna et al., 2010; Buckner et al., 2008; Cavanna and Trimble, 2006). Alterations in activity within the cores of this network (Drevets et al., 2008; Phillips et al., 2003), functional connectivity between nodes in the network and between the DMN and other networks (Kaiser et al., 2015; Mulders et al., 2015) have all been linked to symptoms of MDD. For example, increased connectivity within the anterior DMN has been related to (negative) self-generated thought (rumination) (Berman

* Corresponding author at: Department of Psychiatry, Radboud University Medical Center, Huispost 961, Postbus 9101, 6500 HB Nijmegen, The Netherlands.
E-mail addresses: petercr.mulders@radboudumc.nl (P.C.R. Mulders), philip.vaneijndhoven@radboudumc.nl (P.F.P. van Eijndhoven), joris_pluijmen@hotmail.com (J. Pluijmen), aart.schene@radboudumc.nl (A.H. Schene), indira.tendolkar@radboudumc.nl (I. Tendolkar), c.beckmann@fcdonders.ru.nl (C.F. Beckmann).

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et al., 2011; Connolly et al., 2013; Zhu et al., 2012), while decreased connectivity within the posterior DMN has been related to over-generalizing memory (Zhu et al., 2012).

Changes in connectivity of the DMN differ within several of its subregions. Although functional connectivity within the anterior DMN has consistently been reported to be increased in MDD, results regarding the posterior DMN are conflicting; some studies report an increase (Alexopoulos et al., 2012; Berman et al., 2011; Zhou et al., 2010), while others report a decrease (Zhu et al., 2012), or even areas of both increase and decrease within the same sample (Wu et al., 2011). Understanding the cause of these different results is important, considering that connectivity within the posterior DMN has often been identified as relevant for treatment response in MDD (Andreescu et al., 2013; Li et al., 2013; Wu et al., 2011).

One factor that many studies do not take into account is that the DMN is not static in its spatial topography (Andrews-Hanna et al., 2010). In fact, evidence supports the notion that some areas might be part of the DMN in depression, but not in non-depressed individuals (Andrews-Hanna et al., 2014; Zhou et al., 2010). Additionally, the anterior and posterior subnetworks of the DMN have been shown to dissociate in depressed subjects (De Kwaasteniet et al., 2015; Manoliu et al., 2013; Mulders et al., 2015; Zhu et al., 2012). We hypothesize that inconsistencies in reports about functional connectivity in the posterior DMN could be mediated by differences in the coherence of regions within the DMN in patients with MDD. Exploring new ways to understand the internal organization of the DMN and how it is affected by depression and ECT treatment is therefore crucial to advance research on brain networks in MDD.

Here, we present a novel method of investigating the internal organization of the DMN by looking at the coherence of the different DMN-regions within the network as a whole and show how this method can be used to investigate the state of the DMN in depression, both before and after ECT.

2. Methods and materials

2.1. Participants

Depressed subjects were recruited for this observational cohort study from a pool of patients that were referred for ECT at the Department of Psychiatry of the Radboud University Medical Centre in Nijmegen, the Netherlands. Inclusion criterion was unipolar MDD confirmed using the Structured Clinical Interview for DSM-IV (SCID). Patients were eligible to receive ECT according to the Dutch guidelines for the treatment of depression. This means that before ECT was started their depression was treatment-resistant for selective serotonin-reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants with adjuvant lithium or antiepileptics, as well as psychotherapy. This makes for a more treatment-resistant group when compared to the international literature. All psychotropic medication was discontinued for a minimum of one week prior to ECT, and three weeks for tranylcypromine due to longer washout. No patients received antidepressants with a long lasting half-life prior to the start of treatment. Low doses of promethazine and quetiapine (up to 150 mg) during the course of ECT were allowed, but not in the 24 h before MRI measurements. Depression severity was assessed using the Hamilton Rating Scale for Depression (HRSD, 17 items) before, during and after ECT (Hamilton, 1967). Exclusion criteria were ECT in the year prior to inclusion, bipolar depression, comorbid diagnosis of schizophrenia or substance use disorder, the use of psychotropic medication with the exemption of intermittent benzodiazepine use (not in the 24 h before each ECT session), and MRI-related exclusion criteria. We also recruited healthy control subjects matched for age and sex using local advertisements. The study was approved by the local ethical committee. All subjects provided written informed consent. The treatment itself was unaltered from the standard care for patients receiving ECT.

2.2. ECT-procedure

ECT was administered twice a week bilaterally at the temporal window with a brief pulse, constant current apparatus with a maximum stimulus output of 1008mC (200%) (Thymatron System IV, Somatics, IL, USA). Seizure threshold was determined during the first session with stimulus titration (Lambert and Petty, 1994) and subsequently the stimulus dosage that elicited a seizure was set at 1.5 times the initial seizure threshold. Anesthesia was achieved with intravenous administration of etomidate 0.2–0.3 mg/kg followed by succinylcholine 1.0 mg/kg.

All patients were hospitalized during at least the first two weeks of their ECT course. Treatment was continued until a plateau was reached and no more improvement was seen in the last four bilateral sessions. In line with the Dutch Guidelines for ECT, a minimum of 10 adequate ECT sessions were administered before ECT was stopped in case of non-response or partial response. ECT was terminated before 10 sessions when there was complete remission of all depressive symptoms (van den Broek et al., 2010). A positive response to ECT was defined as a decrease in HRSD-score of 50% or more (Nierenberg and Amsterdam, 1990).

2.3. Image acquisition and preprocessing

Imaging data was acquired using a SIEMENS 1.5T Avanto system. Patients were scanned within the week prior to starting ECT and within one week after their final ECT session. Healthy subjects were scanned at a single timepoint. T1-weighted structural images were obtained using a standard MPRAGE-sequence (T1 850 [ms], TR 2250 [ms], TE 3.68 [ms], flip angle 15 [deg], FoV $256 \times 256 \times 176$ [mm], voxel-size 1.0 [mm] isotropic). Resting-state functional MRI was acquired using an echo planar imaging (EPI) sequence (TR 1870 [ms], TE 35 [ms], flip angle 80 [deg], FoV $224 \times 224 \times 137$ [mm], voxel-size $3.5 \times 3.5 \times 3.0$ [mm], 266 volumes, acquisition time 8 min 20 s). During acquisition of the resting-state data subjects were instructed to lie still with their eyes open and to keep their gaze fixed on a fixation cross while surrounding lights were dimmed. This method has been shown to have the highest reliability and consistency in acquiring resting-state data (Patriat et al., 2013) and promotes the subjects to remain awake during acquisition.

Data was preprocessed using the FMRI Expert Analysis Tool (FEAT), which is part of the FMRIB Software Library (FSL) (Jenkinson et al., 2012). This step includes brain extraction, motion correction, high-pass temporal filtering with a cutoff of 100 s, spatial smoothing with a 6 mm Gaussian kernel, registration of functional images to high-resolution T1 using boundary-based registration and subsequent nonlinear registration to standard space (MNI152). The final voxel size for analysis was 2 mm isotropic. We did not apply global signal regression as this has been shown to induce anti-correlations and potentially distorts group-differences (Murphy et al., 2009; Saad et al., 2012). We used ICA-based Advanced Removal of Motion Artefacts (ICA-AROMA) for further single-subject denoising (Pruim et al., 2015). As head motion is an important factor in fMRI studies, we examined head motion between groups (Satterthwaite et al., 2012; Zeng et al., 2014). Mean displacement for controls, pre-treatment patients and post-treatment patients was 0.33 mm, 0.24 mm and 0.35 mm, respectively. One-way ANOVA revealed no significant differences in motion between the groups ($df=2$; $p=0.22$).