Task-positive and task-negative networks in major depressive disorder: A combined fMRI and EEG study


ARTICLE INFO

Abstract

Background: The study of intrinsic connectivity networks, i.e., sets of brain regions that show a high degree of interconnectedness even in the absence of a task, showed that major depressive disorder (MDD) patients demonstrate an increased connectivity within the default mode network (DMN), which is active in a resting state and is implicated in self-referential processing, and a decreased connectivity in task-positive networks (TPNs), which increase their activity in attention tasks. Cortical localization of this ‘dominance’ of the DMN over the TPN in MDD patients is not fully understood. Besides, this effect has been investigated using fMRI and its electrophysiological underpinning is not known.

Method: In this study, we tested the dominance hypothesis using seed-based connectivity analysis of resting-state fMRI and EEG data obtained in 41 MDD patients and 23 controls.

Results: In MDD patients, as compared to controls, insula, pallidum/putamen, amygdala, and left dorso- and ventrolateral prefrontal cortex are more strongly connected with DMN than with TPN seeds. In EEG, all significant effects were obtained in the delta frequency band.

Limitations: fMRI and EEG data were not obtained simultaneously during the same session.

Conclusions: In MDD patients, major emotion and attention regulation circuits are more strongly connected with DMN than with TPN implying they are more prepared to respond to internally generated self-related thoughts than to environmental challenges.

Major depressive disorder (MDD) is one of the most serious psychiatric diseases in terms of its prevalence rates across the world and illness-related disability (Eaton et al., 2008). The pathophysiology of depression remains poorly understood, firstly, because it is a highly heterogeneous condition and, secondly, because it affects a broad range of motivational, emotional, and cognitive processes, which are difficult to disentangle. Thus, task performance differences between patients and healthy controls may relate to different levels of motivation, rather than attention and information processing per se. The introduction of non-invasive neuroimaging techniques has greatly enhanced our means to understand this illness. The application of these techniques in the so-called ‘resting’ or task-free condition allows to avoid some performance and control confounds and is a powerful approach to measuring the baseline brain activity (Gusnard and Raichle, 2001). The discovery of the so-called resting state or intrinsic connectivity networks (ICN) (Biswal et al., 1995) is considered a landmark in the study of both healthy and diseased brain function. This discovery implies that principal brain functions are not localized in separate brain structures, but are associated with coordinated activity of widespread regions, which show a high degree of interconnectedness even in the absence of a task. Most ICNs increase their activity in tasks associated with externally oriented attention and were called task-positive networks (TPNs), whereas one network shows activity decreases in most kinds of such tasks and was respectively called task-negative network (Fox et al., 2005). Two TPNs are most important for the control of attention – the central executive (CEN) (Seeley et al., 2007) or fronto-parietal control (Vincent et al., 2008) network anchored in the dorsolateral prefrontal cortex (DLPFC) and the salience network (SAL) (Seeley et al., 2007), also called the cinguloopercular network (Dosenbach et al., 2007) anchored in the anterior insula. The task-negative network is usually referred to as the default mode network (DMN) and it includes the precuneus/posterior cingulate cortex (PCC), the medial prefrontal cortex.
of self-focused rumination (Hamilton et al., 2011). Numerous studies have shown that the DMN is related to self-referential processes (Buckner et al., 2008; Raichle, 2015). Because depression is associated with a deterioration of externally oriented attention and an enhanced self-focus (Grimm et al., 2009; Watkins and Teasdale, 2004), it comes as no surprise that MDD patients show an increased connectivity within the DMN and a decreased connectivity in TPNs (Broyd et al., 2009; Greicius et al., 2007; Hamilton et al., 2011, 2013; Marchetti et al., 2012; Menon, 2011; Posner et al., 2013; Sheline et al., 2010). Moreover, an increased ‘dominance’ of the DMN over the TPN in depression patients was found to be associated with the severity of self-focused rumination (Hamilton et al., 2011). Meta-analyses of resting state connectivity studies confirm that the increased connectivity among DMN regions and a hypoconnectivity within the CEN is one of the most reliable findings in MDD patients (Kaiser et al., 2015).

According to the triple network model, changes in the balance of activity and connectivity between the DMN, CEN, and SAL underlie cognitive dysfunction in a number of psychopathological disorders, including the MDD (Menon, 2011). Whereas depression-related changes in connectivity both within- and between- DMN, CEN, and SAL have been found and replicated in many studies, less is known about the cortical localization of the proposed ‘dominance’ of the DMN over the TPN. The evidence of the hyperconnectivity within the DMN and the hypoconnectivity within the CEN, as well as increased connectivity between these networks (Kaiser et al., 2015) is important, but even more important should be evidence about brain regions (both inside and outside these networks), which in MDD patients are more strongly connected with the DMN than with the TPN. This evidence would help to understand where in the brain the proposed depression-related ‘dominance’ of the DMN over the TPN actually takes place. The scarcity of this evidence could be partly explained by the fact that most relevant studies used the independent component analysis (ICA) for extracting the ICNs. This method is well suited for the study of within- and between-network connectivity, but is less convenient than the classical seed-based method for mapping connectivity outside the networks.

Another drawback of existing evidence is that it almost exclusively was obtained based on functional magnetic resonance imaging (fMRI) blood-oxygenation-level–dependent (BOLD) signal, whose relation to neuronal events is still a matter of debate (e.g., Debener et al., 2006). A confirmation of depression-related findings in ICNs connectivity based on electrophysiological data would greatly increase our confidence in the neural origin of respective changes. To the best of our knowledge, only four published studies attempted to test whether fMRI findings of depression-related changes in ICNs connectivity hold true in electrophysiological domain. In two studies, Nugent et al. (2015, 2016) compared ICNs’ connectivity patterns derived using temporal ICA from source space magnetoencephalographic (MEG) time series in MDD patients and controls. They limited the analysis to the beta frequency band and found that patients have reduced connectivity between subgenual anterior cingulate (ACC) and the limbic system and enhanced connectivity between the right insular-temporal region and parts of the limbic system. In another MEG study, Pathak et al. (2016) showed that symptom improvement in MDD patients after rTMS in the DLPFC correlated with increased connectivity between the DLPFC and amygdala, and DLPFC and pregenual ACC in the delta band. Lastly, Knyazev et al. (2016) tested the dominance hypothesis in a nonclinical sample using electroencephalogram (EEG) source-space seed-based correlation analysis and found that depression scores correlated with the dominance of the DMN over the TPN in the right temporal and occipital regions in the delta frequency band. Thus, the first three studies did not directly test the dominance hypothesis and the last one did it in a nonclinical sample. Noteworthy, the last two studies, which analyzed all frequency bands, found the most prominent effect of depression in the delta frequency. There is a good reason to believe that it is not accidental. Delta activity correlates with motivational reward processes (Knyazev, 2012). Specifically, delta oscillations tend to decrease after administration of drugs that induce dopaminergic firing, like cocaine, and increase in states that are associated with the diminishment of dopaminergic activity (Chang et al., 1995; Kiyatkin and Smirnov, 2009; Luoh et al., 1994). Since a diminishment of dopaminergic activity is a distinctive feature of depressive states (Berton et al., 2006; Tremblay et al., 2005), an increase of delta power in MDD patients should be expected. Indeed, many studies have found that depression is associated with an increase of delta power in EEG spectrum (Bjørk et al., 2008; Knott et al., 2001; Korb et al., 2008; Pizzagalli et al., 2004; Saletu et al., 2010; Wacker et al., 2009).

In this study, we aimed to test the dominance hypothesis using seed-based connectivity analysis of resting state fMRI and EEG data obtained in MDD patients and healthy controls. Specifically, based on fMRI and EEG data, we aimed to investigate which cortical areas are more strongly connected with the DMN than with CEN and SAL seeds in depressed individuals as compared to healthy controls. In EEG domain, we expected to find most prominent effect of depression in the delta frequency band.

1. Methods

1.1. Participants

Fifty-seven MDD patients and 36 age-, sex-, and education-matched healthy participants (controls) were initially included in the study. Sixteen patients and 12 controls were later excluded from the analysis due to excessive fMRI or EEG artifacts, thus leaving 41 patients (25 females, mean age 43 years) and 23 controls (13 females, mean age 42 years). Patients with an acute MDD episode were recruited from the inpatient and outpatient clinical departments of the Institute of Physiology and Basic Medicine hospital. The mental health of both groups was initially assessed using an unstructured interview with a psychiatrist according to the ICD-10 criteria (WHO, 1992) and later the severity of depression in patients was additionally assessed using the Structured Clinical Interview for DSM-IV and DSM-V. Exclusion criteria for both groups were major medical illness, history of seizures, pregnancy, a history of substance abuse or dependence, as well as all contraindications against MRI. Exclusion criteria for controls were any current or prior mental health problems. A family history was taken for the healthy subjects to ensure there was no first-degree relatives with any psychiatric disorder. Specific psychiatric exclusion criteria for patients consisted of atypical forms of depression and any additional psychiatric disorder. MDD patients additionally completed the Hamilton Depression Rating Scale and all participants filled in the Beck Depression Inventory (BDI-II) (Beck et al., 1996) and the trait anxiety scale from the State Trait Anxiety Inventory (Spilberger et al., 1970). The study was approved by the Institute of Physiology and Basic Medicine ethical committee and all participants gave written informed consent. Table 1 shows demographic and clinical characteristics of the participants.

1.2. fMRI data acquisition

The resting state functional image scans were acquired on a 3.0-Tesla scanner Discovery MR750w (GE Medical Systems, USA). Participants were instructed to keep their eyes closed without falling asleep. Whole brain resting-state fMRI was acquired for 7.5 min (300 volumes BOLD-EP1 fMRI in axial plane, AP-PC orientation of slices, TR 1.5 s, flip angle 90, TE 30 ms, FOV 220 mm, 64 × 64 matrix size, 33 slices, voxel size 3.4 × 3.4 × 4 mm). High-resolution 1 mm isotropic T1-weighted structural scans (3D FSPGR (BRAVO) in sagittal plane, TR – 9.5 ms, TE – 4.2 ms) were acquired to serve as individual templates.
Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Variables (mean ± SD)</th>
<th>MDD (n = 41)</th>
<th>HC (n = 23)</th>
<th>p valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>16:25</td>
<td>10:13</td>
<td>0.46</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.1 ± 13.8</td>
<td>41.8 ± 7.7</td>
<td>0.67</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>13.2 ± 2.1</td>
<td>12.9 ± 3.4</td>
<td>0.55</td>
</tr>
<tr>
<td>First episode: recurrent</td>
<td>21:20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severityb</td>
<td>6.3 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>7.8 ± 9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of depressive episodes</td>
<td>3.8 ± 5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant free: users</td>
<td>30:11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acutely depressed</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD</td>
<td>17.2 ± 4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDII</td>
<td>30.9 ± 10.9</td>
<td>71.7 ± 7.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>57.1 ± 9.5</td>
<td>44.3 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MDD - major depressions disorder; HC - healthy controls; SD - standard deviation; HAMD - Hamilton Depression Rating Scale; BDII – Beck Depression Inventory II.

a p value for the two-sample t-test of MDD and HC.

b number of DSM-IV MDD criteria met (on basis of DSM-IV interview ranging from 0 to 9)

1.3. fMRI data preprocessing

The preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF, Yan and Zang 2010, http://rfmri.org/DPABI), which is based on Statistical Parametric Mapping (SPM, http://www.fil.ion.ucl.ac.uk/spm) and the toolbox for Data Processing & Analysis of Brain Imaging (DPABI, Yan et al., 2016, http://rfmri.org/DPABI). To account for scanner instabilities, the first ten volumes were discarded. Functional images were slice-time corrected, and normalized to the EPI template in Montreal Neurological Institute (MNI) stereotactic space with a voxel resolution 3×3×3 mm. We checked for motion parameters, which might induce false-positive results (Van Dijk et al., 2012). The cuto-off for motion quality of the images was set at 2 mm for the three translation planes and all participants who exceeded this motion threshold were excluded from the subsequent analysis. We computed individual root-mean-square of the relative displacements between adjacent volumes in mm and compared the groups (Van Dijk et al., 2012). No significant difference between MDD patients and controls was found. The data were spatially smoothed using a Gaussian kernel of FWHM 4 mm.

1.4. Seed-based fMRI connectivity analysis

CONN fMRI functional connectivity toolbox (v17.1, https://www.nitrc.org/projects/conn/) was used for seed-based connectivity analysis of fMRI data. Confounding effects related to white matter/CSF signal as well as motion parameters (six dimensions with first order derivative) were regressed out before the analysis. Functional data were band-pass filtered from 0.01 to 0.10 Hz. Six seeds representing the DMN, CEN, and SAL networks were constructed by forming 10 mm spheres centered at foci identified by the MNI coordinates derived from published fMRI studies. Specifically, DMN was represented by MPF (∼1, −18, −5) and PCC (∼−5, −51, 40) seeds, CEN by left (∼−36, 27, 29) and right (∼36, 27, 29) DLPCP seeds, and SAL by left (∼−32, 24, −6) and right (∼37, 25, −4) anterior insula (Alns) seeds (Dosenbach et al., 2007; Fox et al., 2005; Seeley et al., 2007; Vincent et al., 2008). Maps of Fisher-transformed bivariate correlations between the seed ROI time-course and all other voxels were created and used in the second-level general linear model analyses. The factorial design included one between-subject factor (MDD vs. control) and two within-subject factors – network (DMN, CEN, and SAL) and seed (two seeds for each network). Participant’s age and sex were entered as second-level covariates of no interest. The contrast of interest, which was specified to test the dominance hypothesis, posited that DMN connectivity prevailed over CEN and SAL connectivity in MDD patients, whereas CEN and SAL connectivity prevailed over DMN connectivity in healthy participants.

1.5. EEG data acquisition

Resting EEG data were acquired in the same subjects on a separate occasion. During EEG recording, participants sat in a soundproof dimly illuminated room and were asked to close their eyes and to minimize movements. Six minutes of continuous EEG were obtained for each participant using 118 electrodes mounted in the Quik-Cap128 NSL according to the extended International 10–10 system and the ‘Neuroscan (USA)’ amplifiers with a 0.1–100 Hz analog bandpass filter. The electrooculogram was recorded simultaneously. The sampling rate was set at 1000 Hz. FASTRAK digitizer (Polhemus) was used to measure the position of each electrode and the three fiduciary points (nasion and two preauricular points). Fronto-central electrode was used as the ground and Cz as the reference. Electrode impedances were kept at or below 5 kΩ. EEG data were recomputed to the average reference offline and artifact corrected using independent component analysis via the EEGLab toolbox (http://www.sccn.ucsd.edu/eeglab/).

1.6. EEG data analysis

For EEG data analysis, we used the seed-based oscillatory power envelope correlation analysis in conjunction with beamformer spatial filtering, which has been developed in recent MEG and EEG studies of ICNs (Brookes et al., 2011a, 2011b, 2012; De Pasquale et al., 2010; Hipp et al., 2012; Knyazev et al., 2016, 2017a, 2017b; Siems et al., 2016; Wens et al., 2014). The pipeline of this analysis includes filtering the data into frequency of interest, projecting the filtered data into source space, leakage correction with respect to chosen seed, Hilbert envelope computation, and calculation of correlations between the seed and the rest of the brain (O’Neill et al., 2015). EEG data were frequency filtered into delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–45 Hz) bands using a Butterworth filter and the Matlab’s filtfilt function, which filters the data twice, forwards and backwards to minimize the phase delays, and downsampled to 125 Hz.

Coordinates of the three fiducial points and all the electrodes were used to align the coordinate frame of the EEG data and each subject’s individual sMRI normalized to the MNI space. Locations of the fiducial points were specified on the sMRI volume and an automatic alignment procedure, using an iterative closest point algorithm and the multiple sparse priors method as implemented in the SPM-12 software, non-linearly converged the frames to optimal alignment. The boundary element head model (Fuchs et al., 2001) was used for forward modeling. The cortical mesh consisted of 5124 vertices and was obtained for each subject from his/her sMRI volume. Forward model computation and coregistration were performed using the SPM-12 software (http://www.fil.ion.ucl.ac.uk/spm/). The linearly constrained minimum variance beamforming (Van Veen et al., 1997) was performed using the SPM-12 toolbox for beamforming (DAiSS, https://code.google.com/p/spm-beamforming-toolbox/). Covariance matrices were computed using 5 min continuous eyes-closed EEG data and regularized using a regularization lambda value of 0.05% of the signal variance averaged over channels (Litvak et al., 2010). The time-series of each source was projected along the dipole direction that explains the most variance.

Due to the ill-posed EEG inverse problem, the source-space measurements may be artificially interdependent (Schoffelen and Gross, 2009). Orthogonalization of the reconstructed source time-courses with respect to a seed voxel by means of linear regression is the most frequently used method for signal leakage correction (Hipp et al., 2012; Brookes et al., 2012). After applying this method, the amplitude envelope was calculated as the absolute value of the analytic signal obtained by means of the Hilbert transform and down-sampled to 1-s
time resolution (Brookes et al., 2011b). We used the same seed locations that were used for fMRI data (see above). For individual adjustment of seed locations, we used the method that has been described elsewhere (Knyazev et al., 2017a, 2017b). Briefly, a region of interest (ROI) including all voxels falling within a 10 mm sphere around the seed was determined and the goodness-of-fit (GOF) index was calculated for each ROI’s voxel as the mean z score of all correlations within a respective ICN mask (http://findlab.stanford.edu/functional_ROIs.html) minus the mean z score of all correlations outside it (Greicius et al., 2004). The voxel with maximal GOF was selected for seed location in this subject. Pearson correlations were calculated between the seed and all other voxels, Fisher z-transformed and centered. The obtained connectivity maps were smoothed spatially (FWHM 8 mm) and used in the second-level analyses in SPM12 and SnPM13. For more thorough description of the methods used for seed-based resting state connectivity in EEG/MEG data, see (Brookes et al., 2011a, 2011b, 2012; De Pasquale et al., 2010; Hipp et al., 2012; Knyazev et al., 2016, 2017a, 2017b; Siems et al., 2016; Wens et al., 2014).

1.7. Statistical testing

The issue of proper statistical testing in neuroimaging research is a matter of hot debate. The mass univariate approach is the method of choice in most studies, with inferences usually made at a cluster level after appropriate correction for multiple comparisons (Friston et al., 1994; Nichols and Holmes, 2002). The most widely used fMRI analyses use parametric statistical methods. In a recent paper, Eklund et al. (2016) using real resting-state data and random task group analyses computed empirical familywise error rate (FWE) for the most popular fMRI software packages (SPM, FSL, and AFNI) and a nonparametric permutation method. For a nominal FWER of 5%, the parametric statistical methods have been shown to be conservative for voxel-wise and invalid for cluster-wise inference. By comparison, the nonparametric permutation test is found to produce nominal results in both cases. These findings speak to the necessity of using either more stringent cluster defining thresholds (CDT) (although even at a CDT of \( p = 0.001 \) Eklund et al. found up to 25% false positives), or nonparametric permutation tests. Another issue, raised e.g., in Woo et al. (2014) paper, is the use of liberalcluster-defining primary thresholds (CDPT). Because cluster-extent based thresholding provides low spatial specificity, “researchers can only infer that there is signal somewhere within a significant cluster and cannot make inferences about the statistical significance of specific locations within the cluster” (Woo et al., 2014, p. 412). From a survey of 814 fMRI studies, Woo et al. (2014) show that the overwhelming majority use liberal primary thresholds (e.g., \( p < 0.01 \)), which results in large clusters spanning multiple anatomical regions, making it impossible to reliably infer which anatomical regions show true effects. The recommendation is to use more stringent CDPTs or voxel-wise correction methods for highly powered studies.

On the other hand, one should not underestimate the danger of false negatives. Ultimately, false positives will be sorted out by meta-analytical studies, whereas genuine, but weak false negatives could be lost forever. This danger is particularly high in clinical studies, due to the well-known heterogeneity of clinical groups and uncertainty of diagnostic criteria, which result in high variability and decreased probability of finding significant effects. Therefore, in this study we opted for parallel use of both parametric and nonparametric statistical methods. In the former case, false positive control was implemented through a combination of voxel-level height threshold (CDPT was varied from \( p = 0.01 \) to \( p = 0.001 \) and significant results obtained with most stringent threshold are reported) and cluster-level extent threshold (FWE-corrected cluster-level \( p = 0.01 \)). For fMRI data, nonparametric testing was done using capabilities of the CONN toolbox. For EEG data, group-level random-effects analyses were performed using statistical nonparametric mapping toolbox (SnPM13) (Nichols and Holmes, 2002). In both cases, we used 5000 permutations, CDPT varied from \( p = 0.01 \) to \( p = 0.001 \) and CDT was set at \( p = 0.05 \) (FWE-corrected).

2. Results

The two groups did not differ in age, gender distribution, and education level (all \( p > 0.1, \) see Table 1). About a half of MDD patients had first depressive episode. Most of patients were antidepressant free and all were acutely depressed on the moment of the study (see Table 1).

As a first step of fMRI and EEG data analysis, we tested how well the obtained connectivity maps matched the respective ICNs described in fMRI research. Because different instantiations of ICNs obtained by different methods and in different populations do not match each other perfectly (see e.g., Greicius et al., 2004; Smith et al., 2009), we used two sets of template images. Both were obtained by means of ICA-based analyses. The first one was downloaded from (http://www.fmrib.ox.ac.uk/analysis/brainmap+rsns/) and has been described in Smith et al. (2009). Specifically, we used RSN 4 as DMN template, combined RSNs 9 and 10 as CEN template, and RSN 8 as SAL template (see Smith et al., 2009 for the description and images of these networks). All images were thresholded at \( Z = 3 \). The second set of templates was downloaded from (http://findlab.stanford.edu/functional_ROIs.html) and has been described in Shirer et al. (2011). These images represent binary masks of respective networks. Firstly, we calculated spatial correlations between respective templates from the two sources. These correlations were 0.85 for the DMN, 0.44 for the CEN, and 0.33 for the SAL. Next, for fMRI and EEG data separately, three one-way ANOVAs were performed in the whole sample of subjects (controls and patients combined) with one within-subject factor, which represented DMN, CEN, or SAL by connectivity maps of two respective seeds. The main effect of both seeds was estimated and the false positive control was implemented through a combination of voxel-level height threshold (\( p = 0.001 \) uncorrected) and cluster-level extent threshold (FWE-corrected cluster-level \( p = 0.001 \)). Table 2 shows spatial correlations between thresholded statistical maps and respective templates. As could be expected, these correlations are generally stronger for fMRI than for EEG data. They are also stronger for Smith et al.’s than for Shirer et al.’s templates. In the former case, all correlations are within the range of correlations usually observed in fMRI studies. Thus, Smith et al. (2009) comparing independent components obtained in Brain-Map and resting fMRI data sets reported a minimum correlation \( r = 0.25 \) for 10 maps, which they considered unambiguously paired between datasets. Hence, we may conclude that ICNs derived in our study both from fMRI and from EEG data could be considered a reasonable approximation of respective ICNs described in fMRI studies.

2.1. DMN > CEN&SAL and patients > controls

First, the dominance hypothesis was tested based on fMRI data. Parametric testing of the patients > controls and DMN > CEN&SAL

<table>
<thead>
<tr>
<th>Data</th>
<th>DMN( ^a )</th>
<th>CEN( ^b )</th>
<th>SAL( ^b )</th>
<th>DMN( ^a )</th>
<th>CEN( ^b )</th>
<th>SAL( ^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>fMRI</td>
<td>0.82</td>
<td>0.50</td>
<td>0.33</td>
<td>0.78</td>
<td>0.34</td>
<td>0.30</td>
</tr>
<tr>
<td>Delta</td>
<td>0.42</td>
<td>0.30</td>
<td>0.45</td>
<td>0.35</td>
<td>0.14</td>
<td>0.20</td>
</tr>
<tr>
<td>Theta</td>
<td>0.49</td>
<td>0.32</td>
<td>0.43</td>
<td>0.40</td>
<td>0.17</td>
<td>0.23</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.40</td>
<td>0.33</td>
<td>0.44</td>
<td>0.30</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>Beta</td>
<td>0.30</td>
<td>0.32</td>
<td>0.51</td>
<td>0.21</td>
<td>0.19</td>
<td>0.25</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.29</td>
<td>0.24</td>
<td>0.54</td>
<td>0.17</td>
<td>0.18</td>
<td>0.20</td>
</tr>
</tbody>
</table>

DMN – default mode network; CEN – central executive network; SAL – salience network.

\( ^a \) Smith et al. (2009).

\( ^b \) Shirer et al. (2011).
contrast yielded a significant cluster in the left cerebrum with CDPT 0.002 and FWE-corrected cluster p 0.002 (Table 3, Fig. 1A). Among its 309 voxels, putamen (132 voxels), insula (63 voxels), and pallidum (20 voxels) were most prominently present. The opposite effect (i.e., patients < controls and DMN > CEN&SAL) was not significant. Non-parametric permutation test did not yield significant results. In EEG data, significant effects were obtained only in the delta frequency band. The patients > controls and DMN > CEN&SAL contrast yielded a

### Table 3

Significant clusters revealed in fMRI and EEG data upon evaluation of patients > controls contrasts (controlling for sex and age).

<table>
<thead>
<tr>
<th>Parametric methods</th>
<th>Location</th>
<th>X Y Z</th>
<th>Cl. size</th>
<th>CDPT</th>
<th>Cl. p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMN &gt; CEN&amp;SAL (fMRI)</td>
<td>Putamen, Insula, Pallidum</td>
<td>−30 8 −6</td>
<td>309</td>
<td>.002</td>
<td>.002 N.S.</td>
</tr>
<tr>
<td>DMN &gt; CEN (fMRI)</td>
<td>Putamen, Insula, Frontal pole</td>
<td>−30 38 −12</td>
<td>1416</td>
<td>.01</td>
<td>.01 N.S.</td>
</tr>
<tr>
<td>DMN &gt; SAL (fMRI)</td>
<td>Putamen, Amygdala, Pallidum, Insula</td>
<td>−20 −4 −22</td>
<td>400</td>
<td>.005</td>
<td>.029</td>
</tr>
<tr>
<td>DMN &gt; CEN&amp;SAL (EEG)</td>
<td>MFG, IFG, Insula</td>
<td>−41 38 43</td>
<td>7225</td>
<td>.05</td>
<td>.004</td>
</tr>
<tr>
<td>DMN &gt; CEN (EEG)</td>
<td>MFG, IFG, SFG, Insula</td>
<td>−41 38 39</td>
<td>8302</td>
<td>.01</td>
<td>.011</td>
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<tr>
<td>DMN &gt; SAL (EEG)</td>
<td>IFG, STG, Insula</td>
<td>−27 32 5</td>
<td>7355</td>
<td>.005</td>
<td>.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonparametric methods</th>
<th>Location</th>
<th>X Y Z</th>
<th>Cl. size</th>
<th>CDPT</th>
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<tbody>
<tr>
<td>DMN &gt; CEN&amp;SAL (fMRI)</td>
<td>Putamen, Amygdala, Pallidum, Insula</td>
<td>−20 −4 −22</td>
<td>400</td>
<td>.002</td>
<td>.029</td>
</tr>
<tr>
<td>DMN &gt; CEN (fMRI)</td>
<td>MFG, Insula</td>
<td>−39 32 35</td>
<td>2698</td>
<td>.002</td>
<td>.008</td>
</tr>
<tr>
<td>DMN &gt; SAL (fMRI)</td>
<td>MFG, SFG, Insula</td>
<td>−39 32 35</td>
<td>2303</td>
<td>.003</td>
<td>.029</td>
</tr>
<tr>
<td>DMN &gt; CEN&amp;SAL (EEG)</td>
<td>IFG, Insula</td>
<td>−31 26 5</td>
<td>1749</td>
<td>.002</td>
<td>.030</td>
</tr>
</tbody>
</table>

X, Y, Z represent MNI coordinates of the peak of the cluster.

Cl. size – cluster size in voxels.

CDPT – cluster defining primary threshold.

Cl. p – FWE-corrected cluster p.

DMN – default mode network; CEN – central executive network; SAL – salience network; MFG – middle frontal gyrus; IFG - inferior frontal gyrus; SFG – superior frontal gyrus; STG – superior temporal gyrus.
significantly cluster (CDPT = 0.005, FWE-corrected cluster \( p = 0.004 \)) centered in the left middle frontal gyrus. It covered areas in the left prefrontal cortex including the inferior frontal gyrus and anterior insula (Table 3, Fig. 2A). Nonparametric permutation test yielded very similar effect (Table 3). The opposite effect (i.e., patients < controls and DMN > CEN&SAL) was not significant. Follow-up analyses tested the dominance hypothesis for each TPN separately.

2.2. DMN > CEN and patients > controls

In fMRI data, a significant cluster was found only with CDPT 0.01. As is typical for clusters obtained with liberal CDPT (Woo et al., 2014), it spanned large areas including putamen (269 voxels), insula (164 voxels), and frontal pole (138 voxels) (Table 3, Fig. 1B). The opposite effect (i.e., patients < controls and DMN > CEN&SAL) was not significant. Nonparametric permutation test did not yield significant results. In EEG data, only a marginally significant \( (p = 0.011) \) cluster was revealed using parametric testing with a CDPT of \( p = 0.01 \). This cluster was centered in the left middle frontal gyrus and covered areas in the left prefrontal cortex including the superior and inferior frontal gyri and anterior insula (Table 3, Fig. 2B). Nonparametric permutation test yielded similar cluster with CDPT 0.003 (Table 3). The opposite effect (i.e., patients < controls and DMN > CEN&SAL) was not significant.

2.3. DMN > SAL and patients > controls

In fMRI data, the patients > controls and DMN > SAL contrast yielded a highly significant (FWE-corrected cluster \( p < 0.001 \)) cluster in the left cerebrum with a CDPT 0.002. It included voxels in putamen...
yielded significant effects in vast areas centered in the left middle frontal gyrus, which mostly belong to the dorsal- and ventrolateral prefrontal cortex and are involved in attention regulation circuits. Reduced white-matter fractional anisotropy has been shown in the left middle frontal gyrus of treatment-resistant depression patients, which were significantly improved after rTMS treatment, with these increases being associated with decreased depressive symptoms (Peng et al., 2012). An increased connectivity between lateral prefrontal areas and parts of the DMN has been shown previously in MDD patients and has been described as one of the most distinct findings (Sundermann et al., 2014). Hypoconnectivity within the CEN is also one of the most reliable findings in MDD patients (Kaiser et al., 2015). It seems reasonable to suggest that the effect that has been observed in our study partly reflects a combination of these two effects, because regions in the left prefrontal cortex, which were revealed in MDD patients as the site of increased dominance of the DMN over CEN&SAL, overlap with the left frontal CEN hub. Noteworthy, for the patients > controls and DMN > CEN&SAL contrast, fMRI and EEG effects overlap in the left insular cortex.

For fMRI-based patients > controls and DMN > SAL contrast, in addition to putamen, insula, and pallidum, a significant effect appears in the left amygdala and this is the only effect in fMRI data that survived nonparametric testing. An increased connectivity between amygdala and DMN regions in depressed individuals has been repeatedly reported. Thus, it has been shown that the connection strength between the PCC and the left amygdala (peak voxel: −18, −4, −22; in our study: −20, −4, −22) was a strong predictor of depression scores (Posner et al., 2013). Elevated connectivity of the amygdala with the ACC (Connolly et al., 2013) and the precuneus (Cullen et al., 2014) in MDD patients has also been described. There is also evidence that the functional coupling between amygdala and insula decreases in depressed patients at baseline and increases in the course of antidepressant medication (Chen et al., 2008). Taken together all these pieces of evidence corroborate our finding of depression-related increase of the dominance of the DMN over the SAL in the amygdala. Based on EEG data, the depression-related increase of the dominance of the DMN over the SAL was centered in the left inferior frontal gyrus, but also spread to other areas in the left prefrontal cortex. The localization of this effect was similar to the one observed for the DMN > CEN effect in EEG data. Spatial correlation between the two T-maps was found to be 0.79. In general, the comparison of spatial localization of effects obtained in fMRI and EEG data shows that they include more subcortical structures in the former case and are more superficial in the latter case. This probably stems from the nature of EEG data, which are recorded on the skull and are more sensitive to signals coming from superficial cortical areas than from deep brain sources.

The main strength of this study is that the hypothesis of depression-related predominance of the DMN over the TPN was tested based on both fMRI and EEG data recorded in the same subjects. Results of parallel fMRI and EEG data analyses are reasonably similar, which gives an assurance that they stem from disease-related differences in brain function rather than from artifacts inherent to each method. Some discrepancies in the localization of effects may result from different sensitivity of the two methods to signals coming from different parts of the brain and these results could be treated as complementary rather than contradictory. A limitation of this study is that the patient sample was not homogenous in terms of antidepressant use, depression recurrence, and the duration of illness. Another limitation is a relatively small number of healthy controls. A methodological limitation is that fMRI and EEG data were not obtained simultaneously during the same session. One may expect that if they were, the similarity of results might have been even higher. Next, it should be noted that just two seeds represented each one of the three ICNs. Although it is the usual practice in seed-based connectivity studies and the picked seeds are considered classic DMN, CEN, and SAL nodes (Dosenbach et al., 2007; Fox et al., 2005; Seeley et al., 2007; Vincent et al., 2008), caution should be exercised in interpretation of the reported findings. Thus, the DMN comprises regions more than just the MPF and the PCC. The same applies to CEN and SAL. It is unclear whether the results would stay the same if additional seed regions were included in the analysis. Lastly, in fMRI data, two effects were not confirmed using the nonparametric permutation-based statistical testing and therefore should be interpreted with caution (Eklund et al., 2016). Besides, it should be kept in mind that cluster-extent based thresholding that was used in this study provides low spatial specificity and inferences about the statistical significance of specific locations within the cluster cannot be made (Woo et al., 2014). This particularly relates to clusters revealed in EEG data due to the low spatial resolution inherent to this method.

Summing up, this is the first study, which tested the hypothesis of
depression-related predominance of the DMN over the TPN based on both fMRI and EEG data. Both methods confirmed that in resting condition, DMN in MDD patients is more strongly connected with a set of brain regions than both CEN and SAL together or each of them separately. In EEG, all significant effects were obtained in the delta frequency band, in line with the hypothesis linking these oscillations with motivational processes and pathological conditions (Knyazev, 2012). Our results show that in MDD patients, in resting state, major emotional centers, such as insula, pallidum/putamen, and amygdala, as well as attention regulation circuits in dorsal- and ventrolateral prefrontal cortical areas are more strongly connected with DMN than with TPN seeds implying that they are more prepared to respond to internally generated self-related thoughts than to environmental challenges. It is also worth noting that both fMRI and EEG data point to the left prefrontal cortex broadly defined as the site, which in depressed individuals is stronger connected with the DMN than with the TPN. It is well known from the studies on patients with unilateral cortical damage that depressive symptoms increase following left prefrontal cortex damage (Robinson and Downhill, 1995). It has been suggested that the left prefrontal cortex participates in aspects of positive affect and when damaged leads to hedonic deficits, a hallmark feature of depression (Davidson, 2001). It could be speculated that these left-sided brain areas, which are normally under the control of task-positive networks (meaning they are easily activated by environmental stimuli), in depressed individuals, who are preoccupied with self-focused rumination, fall under the control of the DMN and are not able to respond adequately to environmental cues. However, this hypothesis should be tested in task conditions.

Contributors

GGA and LIA designed the study and wrote the protocol. ANS, AVB, and AES participated in EEG data collection and analyses. IVB, EAO, and EAF managed fMRI data collection and analyses. LIA organized psychiatric diagnostic and expertise. GGA undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

Authors declare no conflict of interest.

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Limitations

A limitation of this study is that the patient sample was not homogenous in terms of antidepressant use, depression recurrence, and the duration of illness. Another limitation is a relatively small number of healthy controls. A methodological limitation is that fMRI and EEG data were not obtained simultaneously during the same session. One may expect that if they were, the similarity of results might have been even higher.


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