Archival Report

Electroencephalography Source Functional Connectivity Reveals Abnormal High-Frequency Communication Among Large-Scale Functional Networks in Depression

Alexis E. Whitton, Stephanie Deccy, Manon L. Ironside, Poomima Kumar, Miranda Beltzer, and Diego A. Pizzagalli

ABSTRACT

BACKGROUND: Functional magnetic resonance imaging studies of resting-state functional connectivity have shown that major depressive disorder (MDD) is characterized by increased connectivity within the default mode network (DMN) and between the DMN and the frontoparietal network (FPN). However, much remains unknown about abnormalities in higher frequency (>1 Hz) synchronization. Findings of abnormal synchronization in specific frequencies would contribute to a better understanding of the potential neurophysiological origins of disrupted functional connectivity in MDD.

METHODS: We used the high temporal resolution of electroencephalography to compare the spectral properties of resting-state functional connectivity in individuals with MDD (n = 65) with healthy control subjects (n = 79) and examined the extent to which connectivity disturbances were evident in a third sample of individuals in remission from depression (n = 30). Exact low resolution electromagnetic tomography was used to compute intracortical activity from regions within the DMN and FPN, and functional connectivity was computed using lagged phase synchronization.

RESULTS: Compared to control subjects, the MDD group showed greater within-DMN beta 2 band (18.5–21 Hz) connectivity and greater beta 1 band (12.5–18 Hz) connectivity between the DMN and FPN. This hyperconnectivity was not observed in the remitted MDD group. However, greater beta 1 band DMN–FPN connectivity was associated with more frequent depressive episodes since first depression onset, even after controlling for current symptom severity.

CONCLUSIONS: These findings extend our understanding of the neurophysiological basis of abnormal resting-state functional connectivity in MDD and indicate that elevations in high-frequency DMN–FPN connectivity may be a neural marker linked to a more recurrent illness course.

Keywords: Default mode network, eLORETA, Frontoparietal network, Lagged phase synchronization, Major depressive disorder, Resting-state functional connectivity

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Major depressive disorder (MDD) is a heterogeneous condition characterized by deficits in emotional, cognitive, and motor functioning. Commensurate with its symptomatic complexity, recent conceptualizations view MDD as a systems-level disorder that arises from dysregulation among large-scale functional brain networks (1–4). Connectivity among these networks has been commonly probed by examining the correlation in blood oxygen level–dependent fluctuations between brain regions under task-free conditions using functional magnetic resonance imaging (fMRI). However, because this is limited to the speed of the hemodynamic response, fMRI-based connectivity is restricted to frequencies < 1 Hz, and it is unclear whether abnormalities in higher frequency neuronal synchronization contribute to connectivity disturbances in depression. This is important because it has been posited that each functional network may be characterized by a unique electrophysiological signature (5,6), and the spectral specificity of this electrophysiological signature may represent a way in which the brain builds a hierarchical structure of interconnected networks (7). Accordingly, differences in the spectral properties of resting-state networks in depression may point to differences in the hierarchical organization of these networks, which may underpin differences in the cross-talk between networks.

Functional networks are spatially distributed sets of brain regions that exhibit temporally correlated activity. Studies have shown that these networks are evident even in the brain’s intrinsic activity during the resting state, termed resting-state...
Abnormal High-Frequency Functional Connectivity in Depression

functional connectivity (rsFC) (8,9). fMRI studies have consistently observed disruptions in the default mode network (DMN) and the frontoparietal network (FPN) in individuals with depression (4). The DMN is composed of regions that exhibit greater activity under task-free conditions relative to conditions requiring goal-directed behavior (10) and include the medial prefrontal cortex, the posterior cingulate cortex and precuneus, and the bilateral inferior temporoparietal cortices and medial temporal lobes (11). This network is thought to subserve self-referential processing, memory, and the allocation of attentional resources for cognitive processing (11). In contrast, the FPN includes a set of brain regions involved in the top-down modulation of attention and emotion and includes portions of the lateral prefrontal cortex and posterior parietal cortex. The FPN is implicated in cognitive control (12) and inhibits the DMN when it is irrelevant to task performance (13). In the context of depression, evidence suggests that abnormal within-DMN rsFC may underlie the tendency for depressed individuals to engage in negative self-referential thought (14), whereas abnormalities in within-FPN rsFC may underpin depression-related cognitive deficits (15). Furthermore, a failure of the FPN to effectively inhibit DMN activity may result in problems shifting attention away from internal thoughts to the external world and is one mechanism that may drive rumination (4,16).

Electroencephalography (EEG) provides a direct measure of postsynaptic potentials with millisecond temporal resolution and a means of studying the high temporal dynamics of functional networks. Approaches to estimating functional connectivity in EEG at the sensor level have been confounded by the diffusion of the EEG signal by the skull; however, advances in source localization (17) have made it possible to minimize these confounds. Although the field is still in its infancy, several groups have begun to examine rsFC using measures of lagged connectivity between EEG source estimates. In applying this method, exact low resolution electromagnetic tomography (eLORETA) (17)—a linear inverse solution—is first used to compute the distribution of current density across voxels in the brain. Next, connectivity between intracortical sources is computed using lagged phase synchronization (LPS). This measure corrects for the effects of volume conduction because it represents the connectivity of two signals after the potentially artifactual zero-lag contribution has been excluded. Importantly, it can be applied to filtered data, allowing for the decomposition of connectivity at individual frequencies.

Findings emerging from studies using this method highlight its promise as a tool for probing the spectral properties of rsFC disturbances. Research has revealed rsFC disturbances within discrete frequency bands in Alzheimer’s disease (18,19), psychosis (20–22), obsessive-compulsive disorder (23), posttraumatic stress disorder (24), and eating disorders (25). To date, only one study has used LPS to examine the spectral properties of connectivity disturbances in MDD (26). This study focused on connectivity between a targeted set of frontal brain regions previously associated with metabolic or anatomical abnormalities in MDD. Individuals with MDD had increased alpha-band LPS between the subgenual anterior cingulate cortex and both the left medial prefrontal cortex and left dorsolateral prefrontal cortex (26). However, these findings are difficult to interpret in the context of an association between increased alpha-band LPS and greater symptom improvement after antidepressant treatment. Furthermore, it remains unknown to what extent altered high-frequency rsFC might represent a state or trait-like marker of MDD.

Therefore, we aimed to capitalize on the high temporal resolution of EEG to investigate the spectral dynamics of rsFC across different frequencies in the DMN and FPN in individuals with MDD. As previous fMRI studies have shown increased within-network connectivity in the DMN and decreased within-network connectivity in the FPN in depression (16), we predicted that relative to healthy control (HC) subjects, individuals with MDD would exhibit stronger rsFC among regions of the DMN and weaker rsFC among regions of the FPN. In addition, given that deficits in emotion regulation in depression are postulated to result from a failure of frontoparietal control systems to regulate DMN activity [indicated by less anticorrelated activity between these networks (4)], we also predicted that individuals with MDD would exhibit stronger between-network rsFC between regions of the DMN and FPN. In light of evidence suggesting that communication among resting-state networks may be driven by synchronization in discrete frequency bands, a critical aim was to determine whether any connectivity abnormalities observed those with MDD were restricted to certain frequency bands. Finally, we compared rsFC in individuals with MDD to an independent sample of individuals in remission from depression (rMDD) to examine the extent to which high-frequency connectivity abnormalities might represent a trait-like vulnerability marker for the condition.

METHODS AND MATERIALS

Participants

Seventy-nine HC subjects and 65 individuals with MDD were recruited from the greater Boston area. In addition, data from a smaller subsample of 30 individuals with rMDD were used in secondary analyses. All participants were right-handed, were between 18 and 65 years of age, had no history of neurological conditions, head injury, or seizures, and were free from recreational substances as indicated by a negative urine drug screen on the day of testing (Amedicheck CLIA-Waved 12-panel cup; Branan Medical Corp., Irvine, CA). Control subjects were eligible if they had no lifetime DSM-IV diagnoses, had no first-degree relatives with psychiatric illnesses, had a Beck Depression Inventory-II (BDI-II) (27) score < 13, and had no lifetime use of psychotropic medication. MDD participants were eligible if they had a current MDD diagnosis according to the Structured Clinical Interview for DSM-IV (28), had been on a stable antidepressant medication over the past 8 weeks or had taken no psychotropic medication for at least 2 weeks (drug-specific washout periods were applied), and had MDD as their primary diagnosis. rMDD subjects were required to have had at least one major depressive episode (MDE) in the past 5 years, to have been in remission for at least 8 weeks as indicated by a score of 1 on the depressed mood and anhedonia items from the Structured Clinical Interview for DSM-IV, and to be free of psychotropic medication (washout periods were applied). Certain past comorbidities were allowed if in remission at the time of testing and secondary to the MDD (see Supplement). All participants provided written informed consent.
**Procedure**

Before EEG, subjects were administered the Structured Clinical Interview for DSM-IV by Masters- or Ph.D.-level clinical interviewers. Those deemed eligible took part in a resting EEG recording on the same day as their Structured Clinical Interview for DSM-IV assessment or shortly thereafter. At their EEG recording, participants completed the BDI-II to assess depressive symptom severity. They also completed the Mood and Anxiety Symptom Questionnaire (MASQ) (29), which yields four subscores: general distress anxious symptoms, general distress depressive symptoms, anxious arousal, and anhedonic depression. In the current sample, the BDI-II ($\alpha = .97$), total MASQ ($\alpha = .86$), and MASQ subscales (general distress anxious symptoms $\alpha = .91$; general distress depressive symptoms $\alpha = .98$; anxious arousal $\alpha = .90$; anhedonic depression $\alpha = .75$) had good internal consistency.

**EEG Recording and Data Reduction**

EEG was recorded using a 128-channel Hydrocel Geodesic Sensor Net system (Electrical Geodesics, Inc., Eugene, OR), sampled at 250 Hz (bandwidth 0.1–100 Hz; impedances $< 100$ kΩ), referenced online to Cz. Data were acquired in eight 1-minute segments (four eyes open, four eyes closed), which were randomized and counterbalanced across participants. Consistent with previous EEG research on depression (30), only eyes-closed data were analyzed. Data processing occurred offline using BrainVision Analyzer 2.0 (Brain Products GmbH, Gilching, Germany). First, muscle artifacts were manually removed, then blinks and electrocardiogram were removed using independent components analysis (31). Because of the influence of independent components analysis correction on coherence measures (32), only components without visible neural activity were removed. Corrupted channels were interpolated using a spline interpolation (33). The EEG was then visually inspected, the remaining artifacts were removed, and it was referenced to the average reference. After processing, nonoverlapping 2.048-second segments were extracted for connectivity analyses. As recommended by Pascual-Marqui et al. (17), all participants had a minimum of 40 seconds of artifact-free data available for analysis.

**Regions of Interest**

Seeds from key regions within the DMN and FPN were selected from the seven-network parcellation described in Yeo et al. (34), and then used to create regions of interest (ROIs) in eLORETA. Given the lower spatial resolution of eLORETA (voxel dimension 5 mm$^3$), bilateral seeds close to the midline were fused into a single seed, and subcortical seeds were omitted. ROIs were created by including all gray matter voxels within a 10-mm radius of the seed. There were ten ROIs from the DMN and nine from the FPN. The Montreal Neurological Institute coordinates for the seeds are listed in Table 1.

**Source-Based Functional Connectivity**

We computed EEG source-based functional connectivity using eLORETA software (17). eLORETA is a linear inverse solution that can reconstruct cortical activity with correct localization from scalp EEG data (17). The solution space consists of 6239 cortical gray matter voxels in a realistic head model (35) using the Montreal Neurological Institute 152 template (36). The LORETA algorithm (upon which eLORETA is based) has been validated in several studies combining LORETA with fMRI (37–39), positron emission tomography (40,41), simultaneous EEG-fMRI (42,43), and intracranial recordings (44).

LPS, a measure that quantifies the nonlinear relationship between two regions after removal of the instantaneous contribution, was then computed across DMN and FPN ROIs. Instantaneous measures of EEG-based connectivity are known to be susceptible to the effects of volume conduction, which can lead to the detection of spurious functional coupling among separate regions. However, lagged connectivity corrects for this because it represents the connectivity between two regions after this zero-lag contribution has been excluded. In this respect, lagged connectivity is considered to represent a true measure of physiological connectivity. LPS between ROIs was computed for each artifact-free EEG segment in the frequency domain using normalized Fourier transforms. Based on previous factor analyses of distinct frequency bands (45), the frequency ranges were: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha 1 (8.5–10 Hz), alpha 2 (10.5–12 Hz), beta 1 (12.5–18 Hz), beta 2 (18.5–21 Hz), and beta 3 (21.5–30 Hz). Additional details can be found in the Supplement.

**Table 1. Seed Coordinates From the Default Mode Network and the Frontoparietal Network**

<table>
<thead>
<tr>
<th>Network</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Anatomical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L DMN-A</td>
<td>–27</td>
<td>23</td>
<td>48</td>
<td>Superior frontal gyrus</td>
</tr>
<tr>
<td>R DMN-A</td>
<td>27</td>
<td>23</td>
<td>48</td>
<td>Superior frontal gyrus</td>
</tr>
<tr>
<td>L DMN-B</td>
<td>–41</td>
<td>–60</td>
<td>29</td>
<td>Angular gyrus</td>
</tr>
<tr>
<td>R DMN-B</td>
<td>41</td>
<td>–60</td>
<td>29</td>
<td>Angular gyrus</td>
</tr>
<tr>
<td>L DMN-C</td>
<td>–64</td>
<td>–20</td>
<td>–9</td>
<td>Middle temporal gyrus</td>
</tr>
<tr>
<td>R DMN-C</td>
<td>64</td>
<td>–20</td>
<td>–9</td>
<td>Middle temporal gyrus</td>
</tr>
<tr>
<td>Mid DMN-D</td>
<td>0</td>
<td>49</td>
<td>18</td>
<td>Medial frontal gyrus</td>
</tr>
<tr>
<td>L DMN-E</td>
<td>–25</td>
<td>–32</td>
<td>–18</td>
<td>Parahippocampal gyrus</td>
</tr>
<tr>
<td>R DMN-E</td>
<td>25</td>
<td>–32</td>
<td>–18</td>
<td>Parahippocampal gyrus</td>
</tr>
<tr>
<td>Mid DMN-F</td>
<td>0</td>
<td>–52</td>
<td>26</td>
<td>Posterior cingulate</td>
</tr>
<tr>
<td>FPN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L FPN-A</td>
<td>–40</td>
<td>50</td>
<td>7</td>
<td>Frontal pole</td>
</tr>
<tr>
<td>R FPN-A</td>
<td>40</td>
<td>50</td>
<td>7</td>
<td>Frontal pole</td>
</tr>
<tr>
<td>L FPN-B</td>
<td>–43</td>
<td>–50</td>
<td>46</td>
<td>Supramarginal gyrus</td>
</tr>
<tr>
<td>R FPN-B</td>
<td>43</td>
<td>–50</td>
<td>46</td>
<td>Supramarginal gyrus</td>
</tr>
<tr>
<td>L FPN-C</td>
<td>–57</td>
<td>–54</td>
<td>–9</td>
<td>Middle temporal gyrus</td>
</tr>
<tr>
<td>R FPN-C</td>
<td>57</td>
<td>–54</td>
<td>–9</td>
<td>Middle temporal gyrus</td>
</tr>
<tr>
<td>Mid FPN-D</td>
<td>0</td>
<td>22</td>
<td>47</td>
<td>Paracingulate gyrus</td>
</tr>
<tr>
<td>Mid FPN-E</td>
<td>0</td>
<td>4</td>
<td>29</td>
<td>Cingulate gyrus</td>
</tr>
<tr>
<td>Mid FPN-F</td>
<td>0</td>
<td>–76</td>
<td>45</td>
<td>Precuneus cortex</td>
</tr>
</tbody>
</table>

Coordinates are in Montreal Neurological Institute space. Labels should be considered approximate because of the uncertain boundaries of the areas and activation patterns.

DMN, default mode network; FPN, frontoparietal network; L, left hemisphere seed; mid, midline seed; R, right hemisphere seed.

**Functional Connectivity Analyses**

Group differences in within- and between-network connectivity were examined by comparing LPS between all pairs of ROIs in the DMN and FPN at each frequency simultaneously.
Analyses were first conducted using t tests that were corrected for multiple comparisons using a nonparametric permutation procedure (5000 randomizations; see Supplement for details). To further probe group differences in connectivity, this was followed-up using a less conservative approach where t values were thresholded at \( p < .001 \) (uncorrected).

**Secondary Analyses**

For connections showing significant group differences, we performed a one-way analysis of variance to evaluate whether any connectivity abnormalities in those with acute MDD were also evident in individuals in remission. In addition, we examined correlations between these connectivity indices and depression severity and illness course. Finally, at the suggestion of a reviewer, follow-up analyses were conducted to determine the extent to which putative group differences generalized to within-DMN and DMN-FPN connectivity more broadly by comparing the MDD and HC subject groups in their mean connectivity of all within- or between-network pairs. Results from these analyses were generally consistent with those reported in the main text and are presented in full in the Supplement.

**RESULTS**

**Sample Characteristics**

Demographic and clinical characteristics are summarized in Table 2. The groups did not differ as a function of sex or education (all \( p \) values > .05). Although the HC and MDD groups did not differ in terms of age, the rMDD group was older than the HC group (\( p = .04 \)). The MDD group scored higher than the HC and rMDD groups on the BDI-II and the four MASQ subscales (all \( p \) values < .001), and it had more lifetime comorbidities than the rMDD group (\( p = .006 \)). Ten subjects in the MDD group were medicated (see Supplement). Within the MDD group, demographic and clinical characteristics did not differ as a function of medication status (all \( p \) values > .05).

### Table 2. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HC (n = 79)</th>
<th>MDD (n = 65)</th>
<th>rMDD (n = 30)</th>
<th>Test Value</th>
<th>Degrees of Freedom</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>58 (73.4)</td>
<td>52 (80.0)</td>
<td>22 (73.3)</td>
<td>( \chi^2 = 0.97 )</td>
<td>2</td>
<td>.62</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>27.5 (8.2)</td>
<td>29.1 (8.4)</td>
<td>32.7 (14.8)</td>
<td>( F = 3.25 )</td>
<td>171</td>
<td>.04</td>
</tr>
<tr>
<td>Education, years, mean (SD)</td>
<td>16.5 (2.5)</td>
<td>16.0 (2.5)</td>
<td>16.5 (2.2)</td>
<td>( F = 0.91 )</td>
<td>171</td>
<td>.41</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>60 (75.9)</td>
<td>41 (63.1)</td>
<td>22 (73.3)</td>
<td>( \chi^2 = 2.97 )</td>
<td>2</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of MDEs, mean (SD)</td>
<td>–</td>
<td>4.1 (4.0)</td>
<td>2.4 (1.5)</td>
<td>( t = 2.16 )</td>
<td>68</td>
<td>.03</td>
</tr>
<tr>
<td>Age at first MDE, mean (SD)</td>
<td>–</td>
<td>19.1 (8.8)</td>
<td>22.2 (12.6)</td>
<td>( t = 1.19 )</td>
<td>68</td>
<td>.24</td>
</tr>
<tr>
<td>Episodes per year since first MDE, mean (SD)</td>
<td>–</td>
<td>0.6 (0.5)</td>
<td>0.4 (0.4)</td>
<td>( t = 1.70 )</td>
<td>68</td>
<td>.09</td>
</tr>
<tr>
<td>Lifetime comorbidities, n (%)</td>
<td>–</td>
<td>37 (56.9)</td>
<td>8 (26.7)</td>
<td>( \gamma^2 = 7.54 )</td>
<td>1</td>
<td>.006</td>
</tr>
<tr>
<td>Current comorbidities, n (%)</td>
<td>–</td>
<td>23 (35.4)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Current psychotropic medications, n (%)</td>
<td>–</td>
<td>10 (15.9)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Symptomatology, Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-II</td>
<td>0.7 (1.6)</td>
<td>26.6 (9.9)</td>
<td>2.8 (3.4)</td>
<td>( F = 331.41 )</td>
<td>171</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MASQ GDD</td>
<td>13.7 (3.3)</td>
<td>37.3 (10.1)</td>
<td>17.6 (6.1)</td>
<td>( F = 213.60 )</td>
<td>171</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MASQ AD</td>
<td>44.3 (10.9)</td>
<td>82.9 (11.2)</td>
<td>48.6 (12.4)</td>
<td>( F = 223.71 )</td>
<td>171</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MASQ GDA</td>
<td>12.8 (2.1)</td>
<td>25.0 (8.3)</td>
<td>14.8 (3.7)</td>
<td>( F = 93.58 )</td>
<td>171</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MASQ AA</td>
<td>17.7 (1.2)</td>
<td>27.7 (9.7)</td>
<td>19.0 (2.9)</td>
<td>( F = 51.20 )</td>
<td>171</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

AA, anxious arousal; AD, anhedonic depression; BDI-II, Beck Depression Inventory-II; GDD, general distress anxious; GDD, general distress depressive; MASQ, Mood and Anxiety Symptom Questionnaire; MDE, major depressive episode.

*Means in a row without a common superscript letter differ as analyzed by one-way analysis of variance (\( p < .05 \)).

**Effects of Acute Depression on Within-Network Connectivity**

Significant differences between the HC and MDD groups emerged for within-DMN connectivity (Figure 1A). The MDD group had stronger LPS between a region in the right superior frontal gyrus (SFG) (corresponds to region R DMN-A in Table 1) and a region in the right parahippocampal gyrus (PHG) (region R DMN-E in Table 1) in the beta 2 frequency band (18.5–21 Hz; \( p < .05 \), familywise error–corrected). Contrary to our hypotheses, there were no group differences in within-FPN connectivity when examined at \( p < .05 \) familywise error–corrected or \( p < .001 \) (uncorrected).

**Effects of Acute Depression on Between-Network Connectivity**

The HC and MDD groups also differed with respect to between-network connectivity (Figure 1B). Specifically, the MDD group showed stronger LPS between a region in the left SFG (region L DMN-A in Table 1) and a region in the right middle temporal gyrus (MTG) (region R FPN-C in Table 1) in the beta 1 band (12.5–18 Hz; \( p < .001 \) uncorrected). Supplemental Figure S1 shows maps of connectivity differences between the MDD and HC groups.

**Clinical Characteristics**

- **Demographics**
  - Female, n (%)
  - Age, years, mean (SD)
  - Education, years, mean (SD)
  - White, n (%)

- **Clinical Characteristics**
  - Number of MDEs, mean (SD)
  - Age at first MDE, mean (SD)
  - Episodes per year since first MDE, mean (SD)
  - Lifetime comorbidities, n (%)
  - Current comorbidities, n (%)
  - Current psychotropic medications, n (%)

- **Symptomatology, Mean (SD)**
  - BDI-II
  - MASQ GDD
  - MASQ AD
  - MASQ GDA
  - MASQ AA
**Abnormal High-Frequency Functional Connectivity in Depression**

**Connectivity After Depression Remission**

To determine whether these abnormalities may be a trait-like marker that persists beyond symptom remission, we compared the indices of beta 2 within-DMN connectivity and beta 1 DMN–FPN connectivity in the MDD and HC groups to an independent sample of rMDD individuals.

A one-way analysis of variance revealed a main effect of group (HC, MDD, and rMDD) for within-DMN beta 2 connectivity between the right SFG and right PHG ($F_{2,171} = 10.01, p < .001, \eta_p^2 = .10$). Bonferroni-corrected pairwise comparisons showed that DMN connectivity was higher in the MDD group relative to both the HC ($p < .001, \text{Cohen's } d = 0.73$) and rMDD ($p = 0.03, d = 0.59$) groups but did not differ between the rMDD and HC groups ($p = 1.00, d = 0.16$).

The same pattern emerged for between-network beta 1 connectivity between the left SFG and right MTG. Specifically, the main effect of group was significant ($F_{2,171} = 9.74, p < .001, \eta_p^2 = .10$), and post hoc tests showed that DMN–FPN connectivity was again higher in the MDD group compared to the HC ($p < .001, d = 0.68$) and rMDD ($p = .008, d = 0.66$) groups, but the rMDD and HC groups did not differ ($p = 1.00, d = 0.03$). These findings did not change when controlling for age (all $p$ values $< .05$), which was higher in the rMDD compared with the HC group. Findings also remained unchanged when medication status was entered as a covariate (all $p$ values $< .05$).

**Associations Between Connectivity Disturbances and Depressive Illness Severity**

When examining the MDD group separately, Spearman’s rank order correlations did not reveal any significant associations between current depressive symptom severity on the BDI-II or MASQ general distress depressive symptoms subscale, and either enhanced within-network DMN connectivity or enhanced between-network DMN–FPN connectivity (all $p$ values $> .05$).

Additional correlations were conducted to examine associations between connectivity disturbances and illness severity in the MDD and rMDD groups. Forty-three MDD subjects and 27 rMDD subjects had information available on their self-reported age of first depression onset and the number of MDEs experienced in their lifetime (Table 2). The groups did not differ in age of onset ($t_{68} = 1.19, p = .24, d = 0.28$); however, the MDD group reported more lifetime MDEs ($t_{68} = 2.16, p = .03, d = 0.58$).

In line with previous research [46], a measure of depressive illness severity was computed as the ratio of lifetime MDEs to the number of years since first depression onset, as a gauge of episode frequency. After computing this, three subjects were excluded from further analyses for having a depressive illness severity score $> 3$ SDs from the mean. Correlations showed greater depressive illness severity was associated with greater beta 1 DMN–FPN connectivity (Spearman’s rank correlation $r = .32, p = .01, N = 67$) (Figure 2). This association remained significant when controlling for current depression severity on the MASQ general distress depressive symptoms subscale (partial $r = .29, p = .02$). This indicates that whereas connectivity disturbances normalized in remitted individuals, for those with a history of depression, a more severe depressive illness course was associated with stronger high-frequency DMN–FPN connectivity.

**DISCUSSION**

Our findings revealed abnormally elevated LPS within the DMN and between regions of the DMN and FPN in individuals with MDD, which emerged in the beta band. Although these connectivity disturbances were not evident in those with rMDD (indicating some normalization after remission), variability in lifetime MDE frequency correlated with between-network connectivity across MDD and rMDD groups. Specifically, enhanced DMN–FPN beta-band connectivity was associated with more frequent MDEs since first depression onset and may
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Figure 2. Scatterplot showing the Spearman rank order correlation between disease severity (operationalized as the mean number of major depressive episodes [MDEs] per year since first depression onset) and the strength of between-network default mode network (DMN)–frontoparietal network (FPN) connectivity (12.5–18 Hz) in the major depressive disorder (MDD) and remitted MDD (rMDD) groups. L, left; MTG, middle temporal gyrus; R, right; SFG, superior frontal gyrus.

therefore be a marker of a more recurrent depressive illness course.

These findings are consistent with those of fMRI studies examining rsFC disturbances in MDD. For example, we observed enhanced LPS between the right SFG and right PHG (regions in the DMN) in the MDD group. These regions overlap with those of a recent fMRI-based meta-analysis, which showed evidence of hyperconnectivity between DMN regions and regions of the hippocampus in those with MDD (4). The PHG is thought to be the primary node in the medial temporal DMN subsystem that mediates connectivity between DMN regions and structures such as the hippocampus that support autobiographical recall (47). Connectivity between the PHG and other DMN regions has been found to become enhanced in depressed individuals during recall of negative events (48). This has also been observed in individuals with rMDD (49) and linked with greater severity of ruminate thoughts, supporting a role for enhanced within-DMN connectivity in rumination. Our observation of enhanced DMN–FPN between-network synchronization in the MDD group, involving the left SFG (DMN) and the right MTG (FPN), also aligns with evidence of enhanced correlation in blood oxygen level–dependent signal between the right MTG and DMN regions (including the left SFG) in depression, which were purported to arise from gray matter abnormalities in the right MTG (50). According to a meta-analysis of fMRI rsFC studies (4) and a recent review on rsFC abnormalities in psychopathology (51), enhanced DMN–FPN connectivity may reflect either a weakness of the FPN to modulate the DMN or the DMN “enslaving” the FPN. Whatever the mechanism, this hyperconnectivity between networks is hypothesized to underpin impairments in goal-directed behavior and a cognitive style that is biased toward internal (often negative), self-referential thoughts.

The convergence of findings across modalities is encouraging; however, a critical question is whether knowledge of the spectral properties of these disturbances tells us something new about MDD pathophysiology. We showed that elevations in LPS within and between networks in the MDD group emerged in the beta band (12.5–21 Hz). The precise processes that beta-band oscillations support remains a topic of debate; however, one view is that beta synchronization promotes the maintenance of a current motor or cognitive state, and is increased in contexts where the brain’s “status quo” is given priority over new signals (52,53). Support for this theory comes from studies showing that pathological enhancement of beta-band synchronization can lead to deterioration of flexible motor and cognitive control. For example, elevated cortico-basal ganglia beta-band synchronization has been linked to impairments in initiating voluntary movement in Parkinson’s disease (54–56), and artificially inducing excessive beta synchronization via intracranial electrical stimulation of the basal ganglia causes the emergence of movement symptoms (57). In light of its predominance at rest, beta-band synchronization has been suggested to correspond to an “idling rhythm” in the motor system (58).

Similarities appear in regard to cognitive functioning and suggest that beta-band synchronization may also correspond to a cognitive idling rhythm. Nonhuman primate studies have shown that synchronization in the beta band is strongest during tasks requiring a high degree of endogenously driven attention and lowest on tasks requiring processing of novel or unexpected external events (59,60). Engel and Fries (52) suggest that strong beta-band synchronization across a neuronal population promotes the maintenance of a motor or cognitive state because the signal of this neuronal assembly overrides any signals coming from new inputs. Building on this, they suggest that the DMN should be distinguished by prominent beta-band synchronization, since it constitutes a state characterized by low expectation of change. Indeed, several studies have revealed positive associations between absolute beta band power and blood oxygen level–dependent signal change in the DMN (5,61–63). In the context of our findings, the elevated beta-band synchronization involving DMN regions in the MDD group may reflect highly synchronized neuronal populations, the signal from which is processed at the expense of other inputs that signal the need to flexibly modulate the DMN in accordance with changing cognitive states. This theory is of course speculative, and future studies (e.g., using neuromodulation techniques to entrain beta oscillations) are needed to directly test whether excessive beta-band synchronization contributes to DMN inflexibility.

These findings demonstrate one of the ways in which studying the spectral properties of connectivity disturbances may provide insight into the neurophysiological origin of network abnormalities in psychopathology, and there are several important avenues for future research. In this study, we conceptualized functional connectivity as a static process involving patterns of phase synchronization that are stable...
across the recording period. However, an emerging field is dynamic functional connectivity (64), which refers to the variability in the strength or spatial organization of connectivity among networks over time. Recent fMRI research shows that in depression, persistent internally focused attention may be linked to decreased variability in connectivity within the DMN (driven by a more persistent positive correlation in activity among regions in the DMN over time), along with increased variability in connectivity between the DMN and regions implicated in regulating attention (65). EEG-based connectivity measures may provide two important extensions to this work: 1) they can reveal how the strength, spatial organization, and spectral properties of connectivity among brain systems converge and diverge over time, and 2) they can capture these changes on a millisecond timescale. If beta-band synchronization is implicated in maintaining cognitive states (particularly the default mode), then one might expect that excessive beta band connectivity would be associated with reductions in dynamic functional connectivity in the DMN.

Some limitations must be kept in mind when interpreting our findings. Several key brain regions implicated in MDD pathophysiology are subcortical, and because eLORETA can only reliably estimate activity in cortical regions, we could not examine connectivity in these regions. In addition, although we observed abnormal rsFC in the beta band in MDD, neural networks likely involve coordinated communication across frequencies (66), and an obvious extension of our work is to examine measures of lagged cross-frequency coupling. Finally, although we used several prerequisite parameters for conducting functional connectivity on EEG source estimates, such as using a high-density EEG montage and a realistic head model (67,68), because of the limitations and inherently low spatial resolution of eLORETA, we cannot rule out that synchronization is implicated in maintaining cognitive states (particularly the default mode), then one might expect that excessive beta band connectivity would be associated with reductions in dynamic functional connectivity in the DMN.

In conclusion, we show that depression is characterized by elevated within-DMN and DMN–FPN phase synchronization in the beta band, which normalizes to some extent after symptom remission but is associated with a more recurrent depressive illness course. Excessive beta-band synchronization, which has been associated with maintaining the brain’s “status quo,” may be a mechanism that drives DMN inflexibility in depressed individuals. These findings highlight measures of EEG source functional connectivity as powerful tools for investigating the spectral signatures of connectivity disturbances in psychopathology.

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REFERENCES


