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# Functional Dysconnection of the Inferior Frontal Gyrus in Young People With Bipolar Disorder or at Genetic High Risk

Gloria Roberts, Anton Lord, Andrew Frankland, Adam Wright, Phoebe Lau, Florence Levy, Rhoshel K. Lenroot, Philip B. Mitchell, and Michael Breakspear

**ABSTRACT**

**BACKGROUND:** Bipolar disorder (BD) is characterized by a dysregulation of affect and impaired integration of emotion with cognition. These traits are also expressed in probands at high genetic risk of BD. The inferior frontal gyrus (IFG) is a key cortical hub in the circuits of emotion and cognitive control, and it has been frequently associated with BD. Here, we studied resting-state functional connectivity of the left IFG in participants with BD and in those at increased genetic risk.

**METHODS:** Using resting-state functional magnetic resonance imaging we compared 49 young BD participants, 71 individuals with at least one first-degree relative with BD (at-risk), and 80 control subjects. We performed between-group analyses of the functional connectivity of the left IFG and used graph theory to study its local functional network topology. We also used machine learning to study classification based solely on the functional connectivity of the IFG.

**RESULTS:** In BD, the left IFG was functionally dysconnected from a network of regions, including bilateral insulae, ventrolateral prefrontal gyri, superior temporal gyri, and the putamen ($p < .001$). A small network incorporating neighboring insular regions and the anterior cingulate cortex showed weaker functional connectivity in at-risk than control participants ($p < .006$). These constellations of regions overlapped with frontolimbic regions that a machine learning classifier selected as predicting group membership with an accuracy significantly greater than chance.

**CONCLUSIONS:** Functional dysconnectivity of the IFG from regions involved in emotional regulation may represent a trait abnormality for BD and could potentially aid clinical diagnosis.

*Keywords:* Bipolar disorder, Genetic risk, Graph theory, Inferior frontal gyrus, Network-based statistics, Resting-state functional connectivity

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Bipolar disorder (BD) is a relatively common and highly disabling condition (1,2) in which causative and pathophysiological underpinnings are poorly understood. The characteristic profile of depressive and manic episodes in BD likely reflects impaired functioning of the neural substrates of emotion regulation and cognitive control. These have been hypothesized to include a constellation of regions in the medial prefrontal cortex (mPFC), the inferior frontal gyrus (IFG), anterior insula, and the dorsolateral PFC (3,4). These regions appear to be crucial for the integration of emotional processing with executive function (5). Dysregulation of the coordinated activity in these regions may thus underlie the phenotypic expression of BD.

Imaging studies of BD have highlighted a particularly key role of the IFG (6). The IFG is involved in a number of cognitive processes of potential relevance to BD, including response inhibition, set switching, socioemotional learning, and sustained attention (7). A meta-analysis of functional magnetic resonance imaging (fMRI) findings in BD found attenuated activation of the IFG across a range of emotional and cognitive tasks (6). Similar findings implicating the IFG are now also emerging in subjects at high genetic risk of BD (8,9). Our group recently reported reduced IFG activation in high-genetic-risk individuals during response inhibition to fearful stimuli in an emotional go-no go task (10). These studies suggest the possibility that loss of the functional integrity of the IFG may underlie trait dysfunction in BD.

A functional disturbance may reflect local, incipient pathology or the compromised ability of that brain region to functionally integrate into larger neuronal circuits (11–13). Resting-state fMRI (rs-fMRI) has proven to be an effective way of assessing the integrity of brain circuits in psychiatric disorders and eschews the need for complex cognitive tasks (14,15). Prior analyses of rs-fMRI data in BD have demonstrated disrupted connections between the PFC and limbic-related structures (16–23). Other studies have documented

 
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altered patterns of functional connectivity within the so-called default mode (24–27), a network of posterior and midline regions that become more active during internally generated cognition (28). To date, there have been three studies of rs-fMRI in psychotic BD patients and their unaffected relatives (29–31). These studies found both shared and unique resting-state network connectivity in probands with psychotic BD or schizophrenia and their unaffected relatives (29–31). Atypical patterns of prefrontal and subcortical intrinsic resting-state connectivity have also been identified in offspring of patients with BD compared with control subjects (32). However, the specific role of the left IFG in mediating risk or expression of BD remains unknown.

We characterized resting-state functional connectivity in BD and those at genetic risk. We focused on a functional cluster within the left IFG for which we recently observed hypoactivation during response inhibition to fearful stimuli in those at genetic risk (10). We undertook three complementary analyses of our rs-fMRI data: network-based statistics (NBS) were used to study group-wise differences in the functional connections between the left IFG and all other gray matter regions (33). We hypothesized that functional connectivity would be selectively diminished between the IFG and regions crucial to emotion and cognitive control in a dose-dependent manner (i.e., the effect will be stronger in those with the established disorder than in those at genetic risk). We also used graph theory to study the complex system-level interactions between the left IFG and the rest of the brain. Whereas NBS captures selective pairwise effects, graph theoretical measures reveal distributed, network-level changes in functional integration and segregation (34). This approach has revealed subtle disturbances in a number of disorders, including functional connectivity in depression (35) and structural connectivity in BD (36,37). We also moved beyond group differences toward diagnostic classification using machine learning. This approach has shown promise in predicting neuropsychiatric classification from neuroimaging data (35,38). In parallel with our between-group contrasts, we thus used a machine learning classifier to investigate whether the functional connectivity of the left IFG could yield diagnostically informative classification.

## METHODS AND MATERIALS

### Participants

Comprehensively phenotyped participants ($n$ = 200) aged 16–30 years comprising three groups were drawn from an ongoing longitudinal study of at-risk individuals: 1) 71 participants genetically at-risk (AR) for BD, 2) 80 matched control (CON) subjects, and 3) 49 BD participants. Details of sample ascertainment, current psychotropic medication, demographic characteristics, and the clinical assessments for younger (16–21 years) and older (22–30 years) age categories are provided in the Supplement.

### Data Acquisition and Preprocessing

Participants were asked to lie quietly in a 3T Philips Achieva (Amsterdam, The Netherlands) scanner with their eyes closed, while 188 functional images were acquired at a repetition time of 2 seconds. Participants were requested to clear their mind to the best of their ability without falling asleep. Preprocessing of data used included realignment, unwarping, anatomical coregistration, and spatial normalization. The functional data were corrected for white matter and cerebrospinal fluid signal. Global signal regression was not performed unless otherwise stated. Further details of image acquisition and preprocessing are provided in the Supplement.

### IFG Region of Interest

We constructed a region of interest (ROI) mask for the left IFG by using a contrast associated with inhibiting a motor response to the perception of a fearful face, as reported in our previous analysis (10). Although centered on the IFG, this cluster also extends into adjacent regions, principally the insula, orbitofrontal cortex, and putamen (Supplemental Figure S1, Supplemental Table S1). We then parcellated the remaining gray matter voxels into 512 contiguous regions of approximately the same volume as this ROI mask (Supplemental Table S2). Mean time courses were extracted from these ROIs, and a functional connectivity matrix of 513 $\times$ 513 pairwise Pearson correlation coefficients was calculated within each subject.

### Network-Based Statistics

To identify between-group differences in functional connectivity we used NBS, a permutation-based method to control familywise error (FWE). We tested for group differences in the strength of functional connectivity between the left IFG and each of the other 512 gray matter parcels. An omnibus $F$ test was first conducted to test for the influence of group. One-tailed two-sample $t$ tests were then calculated to test pairwise differences between the participant groups. All reported sub-networks survive FWE correction ($p < .05$) using a conservative search threshold of $t = 3.75$ (33).

### Graph Theoretical Analysis: Network Metrics

We estimated three network properties of the connections from the IFG to the rest of the brain: 1) the path length (PL); 2) the participation index (PI); and 3) the clustering coefficient (CC). These three metrics were chosen because they capture global (PL), intermediate (PI), and local (CC) aspects of network structure (Figure 3, Supplemental Table S3).

### Classification Using Machine Learning

In parallel with these group-based contrasts, we also sought to study whether the functional connectivity of the IFG could be used to classify participants into their respective groups. We applied support vector classifiers, which are widely used and perform well in many different settings (39), to the functional connectivity of the left IFG. Reduction of this high-dimensional functional connectivity data was performed by recursively removing the least informative functional edges; surviving edges hence represent the most informative features for disambiguating the groups.

## RESULTS

### IFG Functional Connectivity: NBS

The omnibus $F$ test for the left IFG functional connectivity revealed a strong group effect ($p < .0001$ FWE-corrected).