Psychiatry Research: Neuroimaging 231 (2015) 202–209

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Frontal lobe hypoactivation in medication-free adults with bipolar II depression during response inhibition

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ARTICLE INFO

Article history:
Received 18 June 2014
Received in revised form
29 October 2014
Accepted 6 November 2014
Available online 13 November 2014

Keywords:
Bipolar II disorder
Bipolar depression
FMRI
Inferior frontal gyrus
Go/NoGo task
Inhibitory control

ABSTRACT

In executive function, specifically in response inhibition, numerous studies support the essential role for the inferior frontal cortex (IFC). Hypoactivation of the IFC during response-inhibition tasks has been found consistently in subjects with bipolar disorder during manic and euthymic states. The aim of this study was to examine whether reduced IFC activation also exists in unmedicated subjects with bipolar disorder during the depressed phase of the disorder. Participants comprised 19 medication-free bipolar II (BP II) depressed patients and 20 healthy control subjects who underwent functional magnetic resonance imaging (fMRI) while performing a Go/NoGo response-inhibition task. Whole-brain analyses were conducted to assess activation differences within and between groups. The BP II depressed group, compared with the control group, showed significantly reduced activation in right frontal regions, including the IFC (Brodmann's area (BA) 47), middle frontal gyrus (BA 10), as well as other frontal and temporal regions. IFC hypoactivation may be a persistent deficit in subjects with bipolar disorder in both acute mood states as well as euthymia, thus representing a trait feature of bipolar disorder.

1. Introduction

Executive function refers to the complex series of actions required to plan and execute behaviors in a dynamic environment. Essential to this lies both the capacity to choose actions that are appropriate and advantageous to a given situation, while at the same time being able to suppress inappropriate or undesirable behaviors that interfere with one's goals. The neuropsychological literature in patients with bipolar I disorder (BP I) demonstrates impairment during the performance of executive control tasks that is pervasive across all mood states (Malhi et al., 2004, 2007; Martinez-Aran et al., 2004; Henry et al., 2013). Within the domain of executive function, there is evidence of cognitive dysfunction in subjects with bipolar disorder (BP) specifically during the performance of tasks requiring response inhibition (Martinez-Aran et al., 2004; Swann et al., 2009a; Sole et al., 2011; Xu et al., 2012; Henry et al., 2013). Impairment in inhibitory control performance has been observed in subjects with bipolar disorder during mania and euthymia, and it has been shown to be a significant predictor of functional outcomes, including disability severity, quality of life and occupational functioning (Swann et al., 2009b; Reinares et al., 2013).

In healthy control subjects, functional magnetic resonance imaging (fMRI) studies of response inhibition consistently demonstrate the underlying neurobiology to involve activation of the frontal–striatal circuit (Rubia et al., 2001; Aron et al., 2004; Simmonds et al., 2008). The prefrontal cortex (PFC), which includes the dorsolateral prefrontal cortex (DLPFC), orbital frontal cortex (OFC) and the inferior frontal cortex (IFC), plays a central role in executive functioning through its influence on subcortical and posterior cortical regions via extensive anatomical connections to these areas (Croxson et al., 2005; Leh et al., 2007). Recent evidence suggests that successful response inhibition is mediated through striatal dopamine receptors in this frontal–striatal circuit (Ghahremani et al., 2012), and that increased activation of this network is associated with improvement in response-inhibition performance (Congdon et al., 2010).

Earlier fMRI studies of bipolar disorder involving response-inhibition tasks have demonstrated frontal lobe hypoactivation during both the manic and euthymic states (Townsend et al., 2012; Hajek et al., 2013). This suggests that IFC hypoactivation may represent a trait marker of bipolar illness, independent of mood state. However, there are very few imaging studies in depressed subjects with BP and those studies that exist are problematic, as three studies failed to separate BP type I and type II subjects into distinct diagnostic groups (Caligiuri et al., 2003, 2006; Hummer

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http://dx.doi.org/10.1016/j.pscychresns.2014.11.005
0925-4927/

et al., 2013), and a fourth study included only male subjects (Marchand et al., 2007).

The current study sought to explore the neurobiological abnormalities that may exist in participants with bipolar type II (BP II) depression while performing a response-inhibition task. To our knowledge, there are no response-inhibition studies to date that investigate unmedicated adult subjects with bipolar II (BP II) depression. We therefore focused exclusively on a mixed gender adult sample of BP II depressed subjects where results would be unconfounded by medication or heterogeneity of different bipolar subtypes. Based on findings in the literature (Hajek et al., 2013) and earlier research from our group pointing to reduced activation in the Brodmann area (BA) 47 region of the IFC during mania and euthymia (Altshuler et al., 2005; Townsend et al., 2012), we hypothesized that unmedicated depressed adults with BP II disorder would exhibit the same pattern of frontal lobe hypoactivation as seen in other mood states relative to control subjects.

2. Methods

2.1. Participants

The Institutional Review Board at the University of California, Los Angeles (UCLA) approved this study, and each participant provided written informed consent. Subjects with BP II, currently depressed and free of all medications for at least 22 days[1], were recruited through the UCLA Mood Disorders Clinic and local advertising. Healthy control subjects were recruited to the study through local newspaper advertisements and campus fliers.

The Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version (SCID) (First et al., 2002) was administered to all subjects. Those who met criteria for BP II, who were currently in a major depressive episode and scored ≥ 22 on the 30-item Inventory of Depressive Symptomatology-Clinician Rated (Rush et al., 1996), were enrolled. For the current fMRI study, these participants were scanned while unmedicated, before their randomization to treatment in an ongoing clinical trial. Course of illness information (i.e., bipolar illness duration, history of hypomanic and major depressive episodes) was obtained by self-report and confirmed by reference to medical records when available. Participants with a past history of substance abuse or dependence were included only if they were sober for >3 months, as confirmed through self-report and urine toxicology tests. Control subjects were excluded for any current or past psychiatric diagnoses and current medication use. All subjects were excluded for left-handedness, neurological illness, metal implants, head trauma with a loss of consciousness >5 min, certain medical illnesses (e.g., hyperthyroidism), current use of medications with psychotropic effects, or diagnosis of borderline personality disorder, as assessed using the Personality Diagnostic Questionnaire (Hyler et al., 1990) and confirmed via clinical interview. On the day of the scan, severity of hypomania and depression in BP II subjects was assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the 21-item Hamilton Rating Scale for Depression (HAMD-21) (Hamilton, 1960). A seven-item extension of the HAMD (HAMD-28) was used to assess atypical depressive symptoms common in bipolar depression (Rosenthal and Heffernan, 1986).

Twenty-three BP II depressed subjects and 21 age- and gender-matched healthy control (HC) subjects participated, but one HC and four BP II depressed subjects were excluded from further analysis due to excessive movement in the scanner (>3 mm) or susceptibility drop-out. Some subjects used in the present study also performed other tasks in addition to the Go/NoGo task during their MRI scan session, the data from which have been previously reported (Vizueta et al., 2012).

2.2. FMRI imaging procedure

Participants underwent fMRI on a 3-T Siemens Allegra scanner (Siemens, Erlangen, Germany). T2*-weighted, echo planar functional images were acquired using a gradient-echo pulse sequence (repetition time (TR)=2500 ms, echo time (TE)=35 ms, flip angle=90°, matrix 64×64, field of view (FOV)=200 mm, voxel size $3.1\times3.1\times3.0$ mm, slice thickness=3 mm, 1-mm gap, 28 slices). Additionally, high-resolution structural images aligned to the anterior and posterior commissure were acquired with the following parameters: TR=5000 ms, TE=33 ms, flip angle=90°, matrix 128×128, slice thickness=3 mm, 1-mm gap, FOV=200 mm, 28 slices.

[1] One BP subject took one 0.5-mg dose of a benzodiazepine drug 17 days before the scan. Seven BP subjects were medication-naive.

2.3. Activation task

The present fMRI study used a well-validated Go/NoGo paradigm that reliably activates frontal–striatal networks in both healthy controls and BP subjects (Townsend et al., 2012). Stimuli consisted of a sequence of letters presented one at a time via in-scanner goggles. Subjects responded using a button box from which accuracy and response time were recorded. Following an initial 30-s rest block, there were eight alternating 30-s Go and NoGo blocks, with an additional 22.5-s rest at the end. During the rest phases, subjects were shown a white screen with the word "Rest" appearing in the center. Before each Go and NoGo block, a 2-s instruction screen was presented. The Go (control) condition was preceded by the instruction "Press for all letters." During Go blocks, participants were instructed to press the button whenever a letter appeared. The NoGo (experimental) condition was preceded with the instruction "Press for all letters except X." The letter "X" appeared randomly for 25% of trials while the remaining stimuli consisted of other letters. During NoGo blocks, participants were instructed to press the button whenever a letter other than "X" appeared on the screen, or refrain from responding when presented with the letter "X". For each condition (Go and NoGo), stimulus presentation lasted 0.5 s with an inter-stimulus interval of 1.5 s. Before being scanned, participants underwent a separate practice session to familiarize themselves with the task and ensure that they understood the task instructions.

2.4. Demographic data analyses

Statistical analysis of demographic variables was performed using SPSS. Group differences in demographic variables were computed using two-tailed Pearson chi-square and independent *t*-tests. Statistical significance was defined at $\alpha=0.05$.

2.5. Behavioral data analyses

For each group, we computed the means and standard deviations for accuracy and response times for the Go and NoGo conditions. Differences in accuracy and response time were tested independently using two-tailed Fisher's exact tests and Mann–Whitney *U*-tests, respectively. Diagnosis (BP II depression, HC) was used as the between-subject factor. For accuracy, the measures could not be analyzed as continuous variables due to a ceiling effect whereby only a few distinct values were observed. This non-normal distribution was due to the fact that the majority of subjects made few or no errors. As a result, accuracy was dichotomized into two groups (high and low performance) and differences were assessed using Fisher's exact test. Response times also had a non-normal distribution and therefore were analyzed using the Mann–Whitney *U*-test, a non-parametric analogue of the two-sample *t*-test.

2.6. FMRI data preprocessing

Functional MRI images were processed using the fMRI Expert Analysis Tool (FEAT) Version 6.0, part of FSL 5.0.4 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library, www.fmrib.ox.ac.uk/fsl). FSL's Brain Extraction Tool (BET) (Smith, 2002) was used to skull-strip the structural images, and the resulting image was used for intra-subject registration. All scans were examined for motion and/or spike artifacts and data were excluded if motion values exceeded 1 voxel (>3 mm). Motion correction using MCFLIRT (Motion Correction using FMRIB's Linear Image Registration Tool) (Jenkinson et al., 2002) was then performed. To allow for T1 equilibrium effects, the first two volumes of each subject's functional scans were discarded. Spatial smoothing was conducted using a Gaussian kernel of 5 mm full width at half-maximum. Grand-mean intensity normalization (by a single multiplicative factor) and high-pass temporal filtering (using a Gaussian-weighted least-squares straight line fitting, with sigma=60.0 s) were performed. FMRIB's Improved Linear Model was used to perform time-series statistical analyses with local autocorrelation correction (Woolrich et al., 2001). FMRIB's Linear Image Registration Tool (Jenkinson and Smith, 2001; Jenkinson et al., 2002) was used to register functional scans via a two-step transformation. First, functional images from each subject were registered to that subject's co-planar high-resolution skull-stripped structural images using a seven-parameter affine registration and, second, the structural image was aligned to Montreal Neurological Institute (MNI) standard space using a 12-parameter affine registration. Proper registration was confirmed through a manual inspection of all images. In instances where individual co-registrations showed non-linear distortions, degrees of freedom were removed to improve registrations. This procedure was carried out without bias based on group registrations and independent of activation in functional images.

2.7. FMRI data analyses

For the first level analyses, Go and NoGo blocks were modeled separately for each subject. The fMRI statistics were analyzed using the general linear model, with six motion parameter estimates modeled as covariates of no interest. Then