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Authors

Penfold, Conor
Vizueta, Nathalie
Townsend, Jennifer D
et al.

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

Conor Penfold [a], Nathalie Vizueta [a], Jennifer D. Townsend [a], Susan Y. Bookheimer [a,b], Lori L. Altshuler [a,*]

[a] Department of Psychiatry & Biobehavioral Sciences, UCLA Semel Institute for Neuroscience & Human Behavior, Los Angeles, CA 90095, United States
[b] Center for Cognitive Neuroscience, UCLA, Los Angeles, CA 90095, United States

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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

* Corresponding author at: Department of Psychiatry & Biobehavioral Sciences, UCLA Semel Institute for Neuroscience & Human Behavior, 300 UCLA Medical Plaza, Suite 1544, Box 957057, Los Angeles, CA 90095-7057, United States.
Tel.: +1 310 794 9911; fax: +1 310 794 9915.
E-mail address: laltshuler@mednet.ucla.edu (L.L. Altshuler).

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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

contrasts were created to compare activation during the NoGo blocks against the Go blocks to obtain a statistical map for each subject (NoGo minus Go). Additionally, we assessed the presence of task-correlated head motion by correlating each subject's six motion parameters with the three task events (trials when the participant was required to either press a button or inhibit a response or view the visual stimuli). No subjects had significant task-correlated head motion; thus all were included in subsequent analyses.

Higher-level statistics for within- and between-group analyses were conducted using FMRIB's Local Analysis of Mixed Effects stage 1 and stage 2 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). For the whole-brain activation analysis of within- and between-group effects, we report regions with a height threshold of $Z > 2.3$ and cluster probability of $p < 0.05$ corrected (Worsley, 2001). Using Gaussian random field theory, the higher-level analyses were corrected for whole-brain multiple comparisons. The NoGo minus Go contrast was the main focus of these higher level analyses, as this comparison represents activation related to response inhibition.

3. Results

3.1. Subject characteristics

The final analysis included 19 BP II subjects (10 females [52.6%], mean age ± SD = 36.3 ± 12.2 years) and 20 HC subjects (10 females (50%), mean age ± SD = 35.6 ± 11.6 years). There were no significant group differences with respect to age ($t(37) = 0.15$, $p = 0.88$) or gender ($\chi^2(2, n = 39) = 0.27$, $p = 0.87$). See Table 1 for complete clinical demographics in the bipolar group.

3.2. Task performance

Mean accuracy for the Go condition was 97.7 ± 6.2% for the BP II depressed group and 98.4 ± 4.4% for the HC group ($p = 0.74$). For the NoGo condition, mean accuracy was 95.2 ± 4.4% for the BP II depressed group and 96.4 ± 2.8% for the HC group ($p = 0.75$). Go condition reaction times for the BP II depressed subjects were 0.36 ± 0.05 s and 0.40 ± 0.09 s for the HC subjects ($U = 142$, $p = 0.18$).

Table 1
Clinical characteristics for the BP II depressed subjects ($n = 19$)[a].

	Mean	SD
Inventory of Depressive Symptomatology-Clinician rated score	35.9	8.9
Hamilton Depression Rating Scale		
21-item score	18.5	3.4
28-item score	25.2	4.8
Young Mania Rating Scale score	2.6	1.9
Age at illness onset (years)	16.7	7.9
Duration of bipolar illness (years)	18.9	10.9
Duration of current depressive episode (weeks)	16.5	23.1
Lifetime number of major depressive episodes	7.3[b]	5.1
Lifetime number of hypomanic episodes	6.0[c]	6.2
Number of depressive episodes in past 12 months	2.7	1.5
Number of hypomanic episodes in past 12 months	3.0	3.4
Lifetime number of hospitalizations for depression	0.4	0.8
	N	**%**
Current comorbidity		
Posttraumatic stress disorder	2	10.5
Anorexia nervosa	1	5.3
Panic disorder with agoraphobia	1	5.3
Social phobia	1	5.3
Past comorbidity		
Social phobia	1	5.3
Substance use disorders	4	21.1

[a] Inventory of Depressive Symptomatology, Hamilton Depression Rating Scale, Young Mania Rating Scale, Number of depressive episodes in past 12 months, and Number of hypomanic episodes in past 12 months were not available for one bipolar II depressed subject.

[b] Lifetime number of major depressive episodes ranged from 2 to 15; an additional 12 subjects had a number of lifetime episodes scored as "too many to count."

[c] Lifetime number of hypomanic episodes ranged from 1 to 20; an additional 9 subjects had a number of lifetime episodes scored as "too many to count."

Reaction times for the NoGo condition were 0.44 ± 0.06 s for the BP II depressed group and 0.48 ± 0.06 s for the HC group ($U = 122$, $p = 0.06$). Thus, there were no significant between-group differences in response times or accuracy for either the Go or the NoGo condition.

3.3. Blood-oxygen-level dependent (BOLD) fMRI results

3.3.1. Motion artifacts analyses

Analysis of the relative motion ($U = 161$, $p = 0.43$) and absolute motion values ($U = 136$, $p = 0.13$) yielded no significant differences in motion correction between groups. Additionally, the three rotational (roll, pitch, yaw) and three translational (anterior to posterior, superior to inferior, left to right) parameters for each participant were examined to confirm that BP II depressed and HC groups did not differ significantly, which they did not.

3.3.2. Within-group results: Whole-brain analyses

Within-group activation maps for BP II depressed and HC subjects during the NoGo minus Go contrast are displayed in Fig. 1.

HC subjects (Fig. 1A) showed substantial bilateral IFG (BA 47), middle frontal gyrus (BA 9/46 and 10), superior frontal gyrus (BA10) and insula activation $Z > 2.3$, $p < 0.05$, corrected. Control subjects also activated other frontal regions including the left middle frontal gyrus (BA 46 and 6), right middle frontal gyrus (BA 9), left precentral gyrus (BA 6), right cingulate gyrus (BA 32) and right claustrum. For a complete list of regions with significant activation in HC, see Table 2.

The HC group showed temporal lobe activation that occurred exclusively in the right hemisphere involving regions such as the middle temporal gyrus (BA 22 and 21) and superior temporal gyrus (BA 22). Similarly, parietal lobe activation in the HC group occurred only in the right hemisphere, particularly in BA 40 involving both the supramarginal gyrus and the inferior parietal lobule. Occipital lobe activation involved primary and associative visual regions (BA18 and 19) and the inferior temporal gyrus (BA 37). Control subjects exhibited significant subcortical activation, with bilateral activation in the putamen, the thalamus and the right caudate.

Similar to the HC group, there was bilateral inferior frontal gyrus (BA 47) activation during response inhibition in the BP II depressed group. (Fig. 1B displays the within-group activation for the BP II depressed subjects.) Similar to HC subjects, BP II depressed subjects activated right middle frontal gyrus (BA 9/46, 10 and 9), right superior frontal gyrus (BA 10), right cingulate gyrus, right claustrum and bilateral insula. In the temporal and parietal lobes, bipolar II depressed subjects had right hemisphere activity in the superior temporal gyrus (BA 22), supramarginal gyrus and inferior parietal lobule (BA 40). Concerning visual regions, the BP II depressed group activated the right precuneus (BA 19). In subcortical regions, there was activation in the bilateral putamen, right caudate and right thalamus. (See Table 2 for a complete list of coordinates.)

3.3.3. Between-group results: Whole-brain analyses

Between-group results are displayed in Fig. 2 and Table 3. Subjects with BP II depression showed significantly reduced frontal lobe activation compared with HC subjects in the right inferior frontal gyrus (BA 47, 46), right middle frontal gyrus (BA 10, 46, 9 and 6), right superior frontal gyrus (BA 10), right insula and bilateral precentral gyrus (BA 6 and left BA 4/6), $Z > 2.3$, $p < 0.05$, corrected.

Between-group results also revealed significantly reduced activation for BP II depressed subjects compared with HC subjects in the temporal and occipital lobes, including the bilateral middle temporal gyrus, right superior temporal gyrus, left middle occipital gyrus, and the bilateral cuneus and lingual gyrus (see Table 3 for complete between-group results). In the reverse comparison, there were no regions of greater activation in the BP II depressed compared with the HC group.

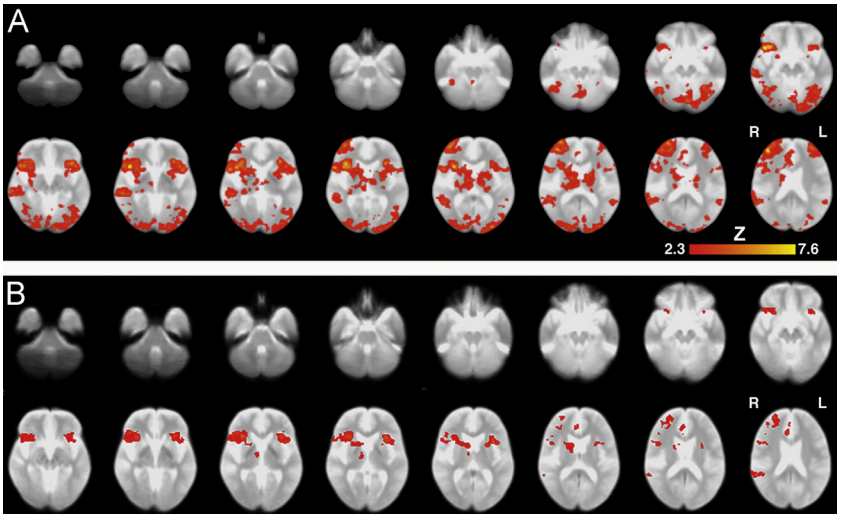

Fig. 1. Within-group results for healthy comparison subjects (A) and medication-free BP II depressed subjects (B) in the NoGo minus Go contrast. Maps are thresholded at $Z > 2.3$, $p < 0.05$ with correction for multiple comparisons. R=right, L=left.

Table 2
Within-group activation results during the NoGo > Go contrast in healthy control ($n=20$) and bipolar II depressed ($n=19$) groups.

	BA	Healthy controls				Bipolar II depressed			
		x	*y*	*z*	*Z*-statistic	*x*	*y*	*z*	*Z*-statistic
Frontal lobe									
L inferior frontal gyrus	47	−38	22	−8	5.70[a]	−36	26	−6	3.19[a]
R inferior frontal gyrus	47	48	18	−10	7.16	44	28	−2	5.12
L middle frontal gyrus	9/46	−38	46	26	6.06[a]				
	46	−32	38	16	3.43				
	10	−36	56	14	4.19				
	6	−32	−6	46	4.53[a]				
R middle frontal gyrus	9/46	42	46	24	6.87	36	32	30	4.00
	10	40	46	20	7.26	30	52	20	3.34[a]
	9	50	6	36	6.80	38	34	36	3.83
L superior frontal gyrus	10	−32	56	24	4.43				
R superior frontal gyrus	10	28	60	24	4.73[a]	26	52	26	4.19[a]
R medial frontal gyrus	8					2	32	42	4.18
L precentral gyrus	6	−52	−2	50	3.83				
R cingulate	32	10	20	32	4.65[a]	4	22	32	4.34[b]
L insula		−32	26	−2	6.56	−30	22	4	4.74[b]
R insula		44	18	−4	7.61[b]	34	18	2	4.96[b]
R claustrum		32	16	2	5.19	28	22	2	5.03
Temporal lobe									
R middle temporal gyrus	22	56	−32	−2	5.27				
	21	64	−28	−8	5.05				
R superior temporal gyrus	22	54	−46	10	5.22	62	−44	12	2.69[a]
Parietal lobe									
R supramarginal gyrus	40	62	−46	36	5.26	66	−48	34	3.91
R inferior parietal lobule	40	52	−42	54	6.17[b]	50	−44	26	4.21[b]
Occipital lobe									
L middle occipital gyrus	18	−30	−94	8	5.85				
R inferior occipital gyrus	37	44	−58	−14	5.44				
L fusiform gyrus	19	−32	−56	−14	4.78[a]				
R precuneus	19	24	−64	44	3.24[a]	26	−62	44	3.98
Subcortical regions									
L putamen		−22	4	8	3.36[a]	−24	8	8	3.71
R putamen		24	8	0	3.70[a]	26	10	8	2.69[a]
R caudate		10	8	4	4.27[a]	12	8	8	3.04[a]
L thalamus		−14	−16	8	4.29				
R thalamus		10	−8	8	4.43[a]	10	−12	4	3.21[a]

(*x*, *y*, *z*) are Montreal Neurological Institute (MNI) coordinates of local maxima significant at $Z > 2.3$ and $p < 0.05$, corrected for multiple comparisons across whole-brain using Gaussian random field theory. BA=Brodmann area; L=left; R=right.

[a] More than one local maxima within 10 mm corresponds to this anatomical label and BA region.
[b] More than one local maxima cluster outside 10 mm corresponds to this anatomical label and BA region.

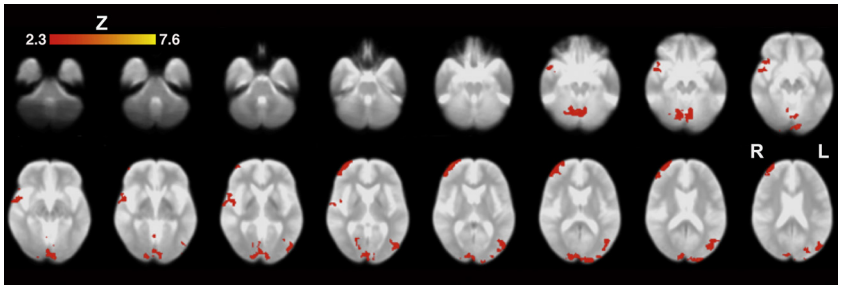

Fig. 2. Between-group results display areas of significantly greater activation in control subjects as compared with unmedicated BP II depressed subjects in the NoGo minus Go contrast (control > BP II depressed subjects). Maps are thresholded at $Z > 2.3$, $p < 0.05$ with correction for multiple comparisons. R=right, L=left.

Table 3
Between-group results for NoGo > Go contrast show regions of significantly greater activation in healthy control compared to BP II depressed subjects.

	BA	*x*	*y*	*z*	*Z*-statistic
Frontal lobe					
R inferior frontal gyrus	47	48	18	−12	3.08
	46	50	44	8	3.43
R middle frontal gyrus	46	50	42	16	3.84[a]
	10	40	60	6	4.02[b]
	9	56	10	44	3.24[b]
	6	42	−4	54	3.21[b]
R superior frontal gyrus	10	42	50	26	3.47
L precentral gyrus/MFG	6	−54	6	38	3.48
L precentral gyrus	4/6	−56	−10	42	3.39[a]
	4	−54	−6	48	3.19
R precentral gyrus	6	54	0	46	3.26[a]
R insula		48	−4	2	3.14
Temporal lobe					
L middle temporal gyrus	19	−40	−80	18	3.89[a]
R middle temporal gyrus	21	54	8	−18	3.97
R superior frontal gyrus	22	56	4	−8	3.85[a]
Occipital lobe					
L middle occipital gyrus	18/19	−20	−100	14	4.17
	19	−50	−76	4	3.49
L middle occipital gyrus	39	−42	−70	12	3.54
L cuneus	18/19	−20	−82	28	3.30
R cuneus	18	8	−94	12	3.63
L lingual gyrus	17/18	−6	−96	−8	3.50[a]
R lingual gyrus	18	2	−90	−8	3.30

(*x*, *y*, *z*) are MNI coordinates of local maxima significant at $Z > 2.3$ and $p < 0.05$, corrected for multiple comparisons across whole-brain using Gaussian random field theory.
BA=Brodmann area; L=left; R=right; MFG=middle frontal gyrus.
[a] More than one local maxima within 10 mm corresponds to this anatomical label and BA region.
[b] More than one local maxima cluster outside 10 mm corresponds to this anatomical label and BA region.

4. Discussion

This study aimed to fill a significant gap in the understanding of response inhibition in adults with bipolar depression, as there is only one other such study in the literature (Hummer et al., 2013). Understanding BP across mood states is essential for identifying neural patterns that may serve as potential trait markers for this disorder. Earlier response-inhibition studies in healthy subjects consistently reported activation of the frontal–striatal circuit. Our control sample demonstrated extensive activation of this same circuit, including bilateral inferior frontal gyrus (IFG), bilateral middle frontal gyrus, bilateral insula, left precentral gyrus and striatal structures, consistent with the literature involving inhibition studies of healthy subjects (Cabeza and Nyberg, 2000; Horn et al., 2003). Many of these same frontal–striatal regions were activated in our medication-free BP II depressed group, but to a significantly lesser extent than in the HC group.

Earlier fMRI response inhibition studies in healthy subjects have shown activation primarily in the right IFC, subthalamic nucleus (STN), and the pre-supplementary motor area (pre-SMA) (Simmonds et al., 2008). These studies are supported by recent connectivity studies that suggest response inhibition results from interactions between the IFC, STN and pre-SMA (Aron, 2007). Anatomical connectivity between the IFC and STN, and between pre-SMA/SMA, STN and the striatum predicts response-inhibition performance (King et al., 2012). Activation of this fronto-basal-ganglia circuit acts to facilitate inhibition of responses that have already been initiated, such as in the NoGo or Stop Signal conditions. The right IFC blocks execution of a Go response via the basal ganglia. One potential mechanism of this inhibition is that activation of the basal ganglia leads to response suppression via increasing the globus pallidus GABAergic (inhibitory) effect of pallidal neurons in the thalamus. Suppression of a thalamic response then leads to suppression (or lack of stimulation) of the motor cortex, which is necessary to block the Go or other prepotent responses (Aron, 2007). Direct parallels between BOLD signal changes and specific alterations in neurotransmitter release have yet to be determined, as reduced regional BOLD signal may result from a variety of factors, including less presynaptic input and more inhibitory presynaptic input from other regions.

Earlier research in mania and euthymia showed decreased IFC activation in BP compared with that in healthy comparison subjects during response inhibition. The current study supports the notion of a bipolar trait effect, specifically in the IFC, during response inhibition, as our group has now found significant attenuation of the right IFC in separate samples of BP subjects in mania (Altshuler et al., 2005), in euthymia (Townsend et al., 2012), and in the current study of depression. Other studies have also reported blunted IFC activation in BP mania and euthymia (Blumberg et al., 1999, 2003; Mazzola-Pomietto et al., 2009). In a study of response inhibition using the stop signal task, significantly less activation in the left IFG (BA 47) and the nucleus accumbens was reported in a medicated sample of adults and youths with bipolar disorder across mood states and combined subtypes I and II compared with healthy controls (Weathers et al., 2012). To our knowledge, there are only two other studies of response inhibition in adult BP depression (Hummer et al., 2013; Radaelli et al., 2013) and both used a Go/NoGo task with emotional and nonemotional stimuli. During the nonemotional contrast, one study reported greater activity in the left putamen in BP manic and euthymic groups compared with the control group (Hummer et al., 2013). However, that study found no between-group differences in any regions, including in the IFG, in the depressed group relative to controls. Another study similarly found no differences between BP I depressed subjects and control subjects, including in IFG activation, during NoGo minus Go conditions with emotional words included as factors (Radaelli et al., 2013). This result was not consistent with the current study's main finding of significant IFG hypoactivation in unmedicated depressed adults with BP II. The discrepancy in results between the studies may be due to differences in BP samples used

(combined BP I and BP II vs. only BP II), differences in medication status and differences in stimuli used. Regarding stimulus type, prior studies used both emotional and nonemotional stimuli whereas the current study only used nonemotional stimuli to avoid potential confounds of processing emotion content.

Consistent with the present study, a recent meta-analysis of BP and response inhibition found that BP patients showed right IFC hypoactivation across mood states (Hajek et al., 2013). The IFC, particularly right lateralized, is a region pivotal to response inhibition, as supported by lesion studies (Aron et al., 2004; Swick et al., 2008; Funderud et al., 2013). This persistent reduction in IFC activation in BP may reflect less activity of neurons involved in inhibition and may help to explain the continued impulsivity symptoms reported in some BP patients even while euthymic (Swann et al., 2001). The etiology of this lack of functional activation remains unknown. Reduced gray matter in the IFC has been reported in several studies (Lopez-Larson et al., 2002; Lyoo et al., 2004; Foland-Ross et al., 2011), and reduced frontal gray matter density may provide an explanation for the functional abnormalities seen in patients with bipolar disorder across mood states. Alternatively, deficits in white matter tracts (Adler et al., 2004; Beyer et al., 2005) or white matter volume (Kieseppa et al., 2003) could also result in a disruption of normal activation in this frontal–striatal circuit. The precise mechanism requires further investigation.

It is of note that IFC hypoactivation in subjects with BP has been observed not only while subjects perform response-inhibition tasks. Bilateral IFC hypoactivation has previously been reported in subjects with BP I while performing emotion-processing tasks during depression (Altshuler et al., 2008) and mania (Foland et al., 2008). The fact that IFC hypoactivation is demonstrated during performance of both response-inhibition and emotion-regulation tasks in BP subjects may not be surprising given the anatomy of this region. Primate studies have shown reciprocal connections between the lateral edge of the OFC and the medial prefrontal emotion-regulatory network (Carmichael and Price, 1995). These regions share extensive reciprocal connections with the amygdala, anterior temporal and anterior cingulate cortex (Ongur and Price, 2000). Functional neuroimaging studies in healthy subjects have demonstrated a role for the medial and lateral sectors of the IFC in mood regulation (Baker et al., 1997; Northoff et al., 2000) and in emotional memory (Cabeza and Nyberg, 2000). It has been speculated that the IFC is involved in the highest level of behavior regulation, including emotion regulation, through pathways between the IFC and autonomic systems that govern visceral responses associated with affective stimuli (Cabeza and Nyberg, 2000). Chronic IFC hypoactivation across mood states and tasks, as well as studies reporting decreased IFC in unaffected subjects at genetic risk for BP (Roberts et al., 2013) and early in the course of BP (Leibenluft and Rich, 2008), further support this as a potential trait marker for BP.

This study has several limitations. First, while the study included a larger sample of BP depressed patients than in recent prior work, it still comprised a relatively small number of patients. As this is the third study of response inhibition in medication-free BP depression, and the only study to control for BP subtype, further studies are required to replicate the findings and clarify the differences between studies. Future studies involving larger numbers of unmedicated BP patients will help elucidate the extent to which the IFC remains hypoactive across mood states and across tasks known to activate the IFC (Brooks and Vizueta, 2014). Second, this study included only BP II depressed subjects, while most studies of bipolar depression focus on BP I or include a combined cohort of BP I and BP II subjects without examining potential differences between these bipolar subtypes. Because the current study included only BP II depressed subjects, its findings cannot necessarily be generalized to BP I depression.

A notable methodological strength of this study is the use of the same Go/NoGo paradigm used in a previous study of BP I euthymic subjects in our laboratory (Townsend et al., 2012), which would facilitate cross-sectional comparisons of mood states across BP I and BP II disorders. Future studies investigating potential differences between BP I and BP II subjects are needed to clarify potential similarities or differences between these subtypes. Another strength is that this study used an unmedicated sample to avoid potential medication confounds. A meta-analysis of studies in BP suggests that psychotropic medications may have normalizing effects on neuroimaging measures that may lead to type II errors, particularly in studies comparing subjects with BP and healthy controls (Hafeman et al., 2012). Future large-scale studies should seek to compare different BP subtypes (for example, type I vs. type II), as well as medication effects on the neural substrates involved in response inhibition.

Right IFC hypoactivation in BP II depression was found in the current study. IFC hypoactivation is also a consistent finding in BP mania and BP euthymia in studies using a variety of response-inhibition tasks. This collective evidence, while in need of larger confirmatory studies, supports the possibility that IFC hypoactivation is a trait marker of bipolar disorder.

Contributors

Dr. Altshuler was the project principal investigator and supervised the collection and analysis of data by Dr. Vizueta. Mr. Penfold preprocessed the data and prepared the first draft of the methods and results sections under the supervision of Dr. Vizueta, with review and contributions by Dr. Bookheimer. Ms. Townsend together with Dr. Altshuler refined the literature review and discussion and wrote the second draft. Dr. Bookheimer provided guidance on the fMRI data analyses and contributed to the first and final drafts.

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