Archival Report

Biological Psychiatry: CNNI

Within- and Between-Session Changes in Neural Activity During Emotion Processing in Unipolar and Bipolar Depression

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ABSTRACT

BACKGROUND: Bipolar disorder (BD) and unipolar depression (UD) can be difficult to distinguish clinically, particularly during episodes of depression. In this study, we test for differences between adults with BD, adults with UD, and healthy control (HC) adults regarding within-session and between-session changes in blood oxygen level–dependent (BOLD) response during implicit emotional processing.

METHODS: During functional magnetic resonance imaging, HC adults ($n = 19$) and adults with UD ($n = 19$) and BD ($n = 16$) performed an implicit emotion processing task. Each participant was scanned twice, separated by 6 months, resulting in 108 scans. The BOLD response and linear change in BOLD response were examined within and between sessions.

RESULTS: We observed within-session linear decreases in BOLD signal (regardless of group, condition, or session) in the left amygdala, a right-sided temporoparietal region, and a right-sided frontoinsular region. We also observed group differences in within-session BOLD signal change ($p < .05$, familywise error corrected) in a left-sided striatoinsular-thalamic region. Adults with BD demonstrated a linear decrease in BOLD signal compared with HC adults ($p < .008$, familywise error corrected) across this region and compared with adults with UD in the posterior insula portion of the region ($p < .008$, familywise error corrected). Finally, we observed main effects of emotional valence in bilateral visuospatial processing regions as well as in the left and right amygdala.

CONCLUSIONS: Adults with BD demonstrated linear attenuation of BOLD response to emotional stimuli within left-sided striatoinsular-thalamic regions. Adults with BD may either have experienced abnormal habituation in this region or have disengaged quickly from processing the emotional stimuli, despite comparable task performance. This pattern may represent an underlying pathophysiologic process associated with BD that differs from UD.

Keywords: Bipolar disorder, BOLD attenuation, Emotion processing, Functional MRI, Major depressive disorder, Whole-brain analysis

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Bipolar disorder (BD) can be difficult to diagnose correctly, particularly during depressive episodes. The delay between initial treatment-seeking and correct diagnosis can span more than a decade (1,2). When a BD diagnosis is made, 17%–27% of individuals are given a misdiagnosis by other treatment providers later in the course of their illnesses (3,4). The potential value of identifying biologically based markers that could help differentiate bipolar and unipolar illness is clear (5,6), and there has been an increase in the number of functional neuroimaging studies aimed at helping to identify such differences (6,7). However, most of this work has examined neural activity as a function of average blood oxygen level–dependent (BOLD) response during a single scanning session. In the present study, we tested for differences between adults with BD, adults with unipolar depression (UD), and healthy control (HC) adults regarding the temporal dynamics of the BOLD response during emotion processing within and between neuroimaging sessions. Examining the dynamics of neural regions involved in emotion processing may provide important information about the pathophysiology of the illness.

Prior neuroimaging work has revealed abnormalities in several key circuits among individuals with BD compared with healthy individuals. Phillips and Swartz (6) identified that individuals with BD demonstrate dysfunction in corticolimbic regions during emotion regulation coupled with hypersensitivity to positive and rewarding stimuli in striatal and frontal reward systems. Abnormalities that can help to differentiate individuals with BD from individuals with UD have been more challenging to identify (7).

Across a small number of studies, differences between UD and BD to positively and negatively valenced emotional faces have been observed in limbic (8–11), subcortical (12), visuospatial (11), and prefrontal regions (10,12). However, different BOLD activity patterns have emerged across studies. For example, in one study from our research group (9), we

observed increased activity in the amygdala to faces displaying a mild sad emotion in individuals with BD relative to individuals with UD, HC individuals, and individuals with BD who were in remission. In another study from our group, using a subsample of the session 1 data analyzed in the present study (11), we similarly observed increased activity to dynamically emerging facial displays of sadness in individuals with BD relative to individuals with UD, but this time in several temporoparietal regions involved in visuospatial processing. By contrast, in a set of studies using pattern classification techniques, Grotegerd *et al.* (10,13) observed the opposite pattern. That is, they found that increased amygdala activation to negative (10) and sad (13) faces was key to accurately classifying individuals with UD, whereas increased amygdala activity to happy faces was more important in classifying individuals with BD.

One way to begin to account for the varied emotional valence effects in neural response between UD and BD is suggested by Grotegerd *et al.* (13), who noted that emotion processing is a dynamic mechanism that unfolds over time. They suggested that different findings may obtain depending on when in that time course the system is probed [see also (14)]. We agree that examining the temporal dynamics of emotion processing is an important next step in the search to identify biomarkers that may differ between UD and BD.

In the present study, we examine differences among adults with BD, adults with UD, and HC adults regarding mean BOLD activity and changes in the BOLD signal that occur between scanning sessions separated by a 6-month interval and changes that occur over time within scanning sessions in response to dynamically emerging positive and negative facial displays. The 6-month interval was chosen to be representative of the durations of typical major depressive episodes (15) and to allow sufficient time for symptom reductions. Following our approach in prior work (9,11,12), and given the above-noted findings, we focused the analyses on between-group differences in the amygdala and across the whole brain. Based on our prior work (9,11), we hypothesized increased mean BOLD response to negative emotions among adults with BD relative to UD across sessions. Whereas we expected to observe attenuation of the BOLD signal across groups and conditions in regions involved in emotional processing, including the amygdala (potentially representing habituation effects over time), based on related findings from previous work (13), we expected to observe greater attenuation of BOLD signal to happy faces among the adults with UD versus BD, both within and between sessions. Finally, an exploratory aim of this study was to examine the degree to which changes in brain activity across sessions tracked with changes in symptoms. We expected that normalization of brain function in patient groups would be associated with symptom reduction.

METHODS AND MATERIALS

Participants

The 57 participants for the present study were a subset of individuals who participated in a larger examination of neural differences between BD and UD (R01-MH076971, MLP principal investigator). The current sample represents individuals who were scanned at an initial visit (session 1) and who were scanned again 6 months later (session 2): 21 currently depressed adults with a diagnosis of UD, 17 currently depressed adults with a diagnosis of BD, and 19 HC adults. All participants were right-handed, all were native English speakers, and all were screened with the Structured Clinical Interview for Psychiatric Disorders (16). In all diagnostic groups, participants were excluded if they had a history of head injury, systemic medical illness known to interfere with blood flow or brain function, cognitive impairment (score <24 on Mini-Mental State Examination) (17), color blindness, premorbid IQ estimate <85 (18), psychosis (including any psychotic mood symptoms), borderline personality disorder (19), and standard magnetic resonance imaging (MRI) exclusion criteria (e.g., metallic objects in the body). Participants in the UD and BD groups were also excluded if they met criteria for an alcohol or substance use disorder within 2 months before the scan. For the HC group, additional exclusion criteria included any current or prior alcohol or substance use disorder and any personal or immediate-family history of an Axis I disorder. All participants in all groups were required to pass urine drug screens and breath alcohol tests before both scanning sessions. In the original project from which these

Table 1. Demographics and Behavior

Variable	UD Group (n = 19)	BD Group (n = 16)	HC Group (n = 19)	Effect of Group	Post hoc
Demographics					
Women	78.95%	93.75%	57.89%	$\chi^2_2 = 6.26$[a]	BD > HC[a]
Age, years	32.53 (7.24)	35.22 (8.91)	32.17 (6.28)	$F_{2,51} = 0.84$	
IQ (NART estimate)	111.34 (10.29)	114.10 (8.84)	113.19 (7.68)	$F_{2,51} = 0.43$	
Behavior (Session 1)					
Accuracy	95.32% (4.94%)	92.84% (7.01%)	96.86% (3.00%)	$\chi^2_2 = 4.14$[b]	
Reaction time	959.72 (145.96)	997.57 (154.16)	948.70 (185.44)	$\chi^2_2 = 1.63$[b]	
Behavior (Session 2)					
Accuracy	94.48% (5.78%)	93.97% (7.64%)	92.03% (7.76%)	$\chi^2_2 = 1.07$[b]	
Reaction time	961.04 (161.06)	985.65 (184.55)	941.66 (106.96)	$\chi^2_2 = 0.15$[b]	

Values are presented as mean (SD) or %.
BD, bipolar disorder; HC, healthy control; NART, National Adult Reading Test; UD, unipolar depression.
[a]$p < .05$.
[b]Owing to nonnormality, the nonparametric Kruskal-Wallis test was used for comparisons.