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An fMRI study of attentional control in the context of emotional distracters in euthymic adults with bipolar disorder

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ABSTRACT

Inability to modulate attention away from emotional stimuli may be a key component of dysregulated emotion in bipolar disorder (BD). Previous studies of BD indicate abnormalities in neural circuitry underlying attentional control, yet few studies examined attentional control in the context of emotional distracters. We compared activity and connectivity in neural circuitry supporting attentional control and emotion processing among 22 individuals with BD type 1, currently remitted and euthymic, and 19 healthy controls. Participants performed an emotional n-back paradigm, comprising high and low attentional demand conditions, each with either emotional (happy, fearful), neutral or no face flanker distracters. During the high attentional control demand conditions without emotional distracters, BD individuals showed reduced activity relative to controls in dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (dACC), and inferior parietal cortex. During the high attentional control demand conditions with fearful-face distracters, BD individuals showed greater activity than controls in these regions and amygdala and striatum. Relative to controls, BD individuals also showed abnormal patterns of effective connectivity between dACC and amygdala during high attentional control demand with emotional face distracters. Inter-episode bipolar disorder is characterized by abnormal recruitment of attentional control neural circuitry, especially in the context of emotionally distracting information.

1. Introduction

Bipolar disorder (BD), one of the 10 most debilitating illnesses worldwide (World Health Organization, 2004), is characterized by a central deficit in the ability to regulate emotion (Goodwin and Jamison, 2007). Importantly, this deficit may persist even during remission (Phillips et al., 2003); thus, examining the neural basis of emotion dysregulation in BD may advance understanding of key pathophysiologic processes of the illness. The ability to flexibly redirect attention (i.e., attentional control) away from emotionally distracting stimuli represents an important component of emotion regulation that may be deficient in BD (Phillips et al., 2008a).

Attentional control entails 1. selective attention toward goal-relevant stimuli, and 2. redirection of attention away from distracting, goal-irrelevant stimuli (Phillips et al., 2008a). Attentional control is fundamental to a range of cognitive tasks, including working memory (Gazzaley, 2010), sustained attention (Braver et al., 2003), and attentional set shifting (Nagahama et al., 2001). Maintaining attention to pertinent information is particularly challenging in the presence of distracting emotional stimuli, which compete for cognitive resources (Luo et al., 2007). Distributed prefrontal and parietal–cortical, anterior cingulate-cortical, and striatal-thalamo circuitry mediates attentional control (Alexander and Crutcher, 1990; Bush and Shin, 2006). Furthermore, maintaining attention in the presence of emotional distracters is dependent on this circuitry (Bishop et al., 2004; Dolcos and McCarthy, 2006; Erk et al., 2007; Goldstein et al., 2007) and intact functional coupling between prefrontal and anterior cingulate cortices and amygdala (Etkin et al., 2006; Urry et al., 2006).

Attentional control deficits have been documented among BD individuals using tests of sustained attention (Clark et al., 2002, 2005; Maalouf et al., 2010) and working memory (Martínez-Arán et al., 2005; Thompson et al., 2007). Neuroimaging studies

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employing working memory paradigms reported reduced (Lagopoulos et al., 2007; Monks et al., 2004; Townsend et al., 2010), but also increased (Adler et al., 2004), activity in prefrontal attentional control circuitry in BD individuals relative to controls. Studies using the Stroop color-word selective attention task reported reduced activity in BD individuals vs. controls in ventral prefrontal regions (Blumberg et al., 2003; Kronhaus et al., 2006; Strakowski et al., 2005) and anterior cingulate cortex (ACC) (Gruber et al., 2004), although greater activity in dorsolateral prefrontal cortex (dlPFC) (Gruber et al., 2004). Although some inconsistencies remain, these findings suggest that attentional control deficits among BD individuals may reflect diminished recruitment of underlying attentional control neural circuitry.

Paradigms with intersecting cognitive and emotional demands may be particularly relevant to BD, given the aforementioned attentional control deficiencies and consistent findings of abnormally increased activity in subcortical regions supporting emotion processing among BD individuals (Altshuler et al., 2005; Almeida et al., 2010; Hassel et al., 2008, 2009; Lawrence et al., 2004). The few studies in this area have provided conflicting results, with some studies indicating that BD individuals show abnormally *elevated* activity in attentional control prefrontal cortical (Deckersbach et al., 2008; Elliott et al., 2004; Wessa et al., 2007) and in emotion processing subcortical (Wessa et al., 2007) circuitry during cognitive task performance with emotional distraction, while others have found abnormally *reduced* activity in attentional control circuitry relative to healthy controls (Malhi et al., 2005; Strakowski et al., 2005; Lagopoulos and Malhi, 2007). Several factors likely contributed to these discrepancies, including the use of different paradigms, unequal between-group task performance (Malhi et al., 2005), and recruitment of BD individuals in different mood states. Furthermore, while all of the tasks used in these studies required attentional control, they addressed slightly different domains of executive functioning, from response inhibition (e.g., affective Go/No-Go; Elliott et al., 2004; Wessa et al., 2007), set shifting (e.g., emotional Stroop; Lagopoulos and Malhi, 2007; Malhi et al., 2005), to working memory (Deckersbach et al., 2008), each engaging partially distinct patterns of cortical activation. Another factor is the use of different types of emotionally distracting stimuli, from emotional words (Elliott et al., 2004; Wessa et al., 2007), to pictures (Strakowski et al., 2011), to induced negative mood (Deckersbach et al., 2008). Also noteworthy is that some studies employed only negative emotionally distracting information (Deckersbach et al., 2008), while other used negative emotional and neutral distracters (Lagopoulos and Malhi, 2007; Strakowski et al., 2011), or negative and positive emotional distracters (Elliott et al., 2004; Malhi et al., 2005; Wessa et al., 2007). Further research is clearly required to elucidate possible neural system abnormalities among BD individuals during cognitive tasks requiring redirection of attention away from emotional distracters.

Given that attentional control is mediated by distributed neural circuitry, connectivity analyses are a natural extension of this literature. Functional connectivity (FC) measures correlations over time between activity in different neural regions, while effective connectivity (EC) measures the impact of activity in one region over another (Roebroeck et al., 2005). Thus far, studies employing these techniques in BD have used emotion processing paradigms, and reported decreased amygdala-vlPFC FC (Foland et al., 2008), decreased amygdala-ACC FC (Wang et al., 2009), increased parahippocampal-subgenual cingulate cortical EC (Almeida et al., 2009a), and reduced vmPFC-amygdala EC in BD individuals vs. controls (Almeida et al., 2009b). One study also described decreased resting state amygdala-VPFC FC among BD individuals relative to controls (Chepenik et al., 2010). In the current study, we employed the *Emotional Face N-Back* (EFNBACK) task, a paradigm requiring direction of attention away from emotional (fearful and happy) and neutral-face distracters to perform an n-back working memory task (Ladouceur et al., 2009). The paradigm also includes a no-distracter, attentional control condition. We previously showed slower task performance on the attentional demand condition with fearful-face distracters in high trait anxiety individuals at risk of mood disorders (Ladouceur et al., 2009), and significantly greater dlPFC activity to this condition in remitted individuals with a history of major depressive disorder (Kerestes et al., 2012). We used a region of interest (ROI) approach to examine differences in activity and EC between BD individuals and controls within: 1. attentional control neural circuitry: prefrontal and parietal cortices, ACC and striatum during attentional control; and 2. this neutral circuitry and the amygdala, a key emotion processing region, during attentional control in the context of emotional distracters. The EFNBACK has two important features, the combination of which distinguishes it from previous paradigms examining attentional control in the context of emotional distracters in BD. First, the distracters in this task are distinct from the stimuli comprising the attentional control component (unlike, for example, affective Go/No-Go tasks). Second, the paradigm includes neutral, positive, and negative emotional distracters, enabling us to comprehensively examine neural circuitry supporting attentional control vs. attentional control in the context of different types of emotional and neutral distracting stimuli. Furthermore, we examined neural circuitry when task performance was equivalent across groups, to avoid the potential confound of poor task performance upon neural activity of some studies in BD (Adler et al., 2004; Gruber et al., 2004; Malhi et al., 2005; Strakowski et al., 2005; Thermenos et al., 2010). We examined remitted, euthymic BD individuals to identify functional neural abnormalities that were mood state independent.

We formulated the following hypotheses based on the collection of previous attentional control studies in BD, as well as the neural model of emotion regulation deficits in BD previously described by our group (Phillips et al., 2008a). This model highlights the role of abnormal dorsolateral, ventrolateral and dorsomedial (including dACC) prefrontal cortices activity during voluntary regulation of attention away from emotional distracters among BD individuals. In light of previous studies of attentional control neural circuitry in BD (Blumberg et al., 2003; Kronhaus et al., 2006; Lagopoulos et al., 2007; Monks et al., 2004; Strakowski et al., 2004), we hypothesized that BD individuals would show *reduced* activity in attentional control neural circuitry vs. controls, particularly in dlPFC and dACC, during the no-distracter, attentional control condition. We hypothesized that during attentional control in the context of emotional distracters, BD individuals would show abnormally *elevated* activity in this circuitry and amygdala vs. controls, given that the only previous study of euthymic BD individuals using a paradigm employing both positive and negative emotional distracters documented *greater* activity in BD vs. healthy individuals (Wessa et al., 2007). Exploratory analyses compared EC between neural regions in attentional control circuitry and the amygdala during attentional control in the context of emotional distracters in BD individuals vs. controls.

2. Materials and methods

2.1. Participants

The study was approved by the Institutional Review Board at the University of Pittsburgh. All individuals provided written informed consent before participation. 41 participants (aged 19–46 years): 22 individuals with bipolar I disorder (Structured Clinical Interview for DSM-IV, Research Version (SCID-P) (First et al., 1995) criteria), and 19 healthy controls without previous personal or family history of