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Functional connectivity during masked and unmasked face emotion processing in bipolar disorder

Wan-Ling Tseng[a,*], Laura A. Thomas[b], Elizabeth Harkins[a], Joel Stoddard[a], Carlos A. Zarate Jr[c], Daniel S. Pine[a], Ellen Leibenluft[a], Melissa A. Brotman[a]

[a] Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA
[b] War Related Illness and Injury Study Center, Veterans Affairs Medical Center, Washington, DC, USA
[c] Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

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ABSTRACT

Little is known regarding the neural connectivity and correlates during automatic, *unconscious* face emotion processing in individuals with bipolar disorder (BD). In this study, 14 adults with BD and 14 healthy volunteers (HV) underwent fMRI scanning while completing an affective priming task with unconsciously perceived and consciously perceived faces (angry, happy, neutral, blank oval). We found that, regardless of awareness level and emotion types, BD patients exhibited *diminished* functional connectivity between amygdala and ventromedial prefrontal cortex (vmPFC) compared to HV. This connectivity finding is present in the absence of activation differences in amygdala. In addition, in medial frontal gyrus, BD patients displayed *greater* activation while HV displayed *less* activation to angry and neutral faces compared to blank ovals. These results suggest that aberrant amygdala-vmPFC connectivity and neural dysfunction in areas implicated in appraisal and expression of emotions (medial frontal gyrus) may be the pathophysiological correlates of emotional processing in BD regardless of awareness level.

1. Introduction

Neural dysfunction while processing face emotions represents one of the best-replicated pathophysiological findings in the literature on bipolar disorder (BD) (for reviews and meta-analyses, see Blond et al., 2012; Chen et al., 2011; Delvecchio et al., 2012; Houenou et al., 2011; Kupferschmidt and Zakzanis, 2011; Strakowski et al., 2012). This line of research, however, has focused on consciously perceived face emotions (i.e., unmasked faces presented ≥40 ms) across implicit (e.g., labeling gender of emotional faces) and explicit paradigms (e.g., labeling emotions of emotional faces). Few studies have probed automatic, unconscious face emotion processing using masked faces (i.e., faces presented < 40 ms) in individuals with BD (Grotegerd et al., 2014; Thomas et al., 2014). Additionally, to our knowledge, no study has examined functional connectivity during this early stage of emotional processing.

Employing masked face processing paradigms is important because prolonged viewing of emotional faces, required for explicit and implicit tasks, may obscure neural dysfunction that occurs unconsciously during early, rapid processing of emotions (Monk et al., 2008; Nomura et al., 2004). Such aberrant automatic face processing may contribute to mood dysregulation and interpersonal difficulties that often occur without subjective awareness or insight in individuals with BD. Research in healthy adults and adults with anxiety and mood disorders has implicated several brain regions underlying automatic, unconscious face processing, including the amygdala, anterior cingulate cortex, inferior frontal gyrus, and occipito-temporal visual cortical regions (e.g., Killgore and Yurgelun-Todd, 2004; Lichev et al., 2015; Morris et al., 1998; Suslow et al., 2009; Whalen et al., 1998). Regarding connectivity, higher amygdala-thalamus functional connectivity was found in women with borderline personality disorder compared to healthy women (Cullen et al., 2011). A lack of coupling of metabolic activity between the orbital frontal cortex and amygdala was observed in patients with borderline personality disorder and Intermittent Explosive Disorder relative to controls (New et al., 2007). Here, we expand the literature to adults with BD by examining neural connectivity and activation during face emotion processing both above and below awareness level.

* Correspondence to: Emotion and Development Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Building 15, Room 208, 15K North Drive, Bethesda, MD 20892, USA.
E-mail address: wan-ling.tseng@nih.gov (W.-L. Tseng).

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Research using consciously perceived face emotions has implicated functional abnormalities in the fronto-limbic network in BD (e.g., Brotman et al., 2014; Chen et al., 2011). However, despite consensus in the literature that BD is associated with disrupted fronto-limbic connectivity (Strakowski et al., 2012), relatively few studies have investigated functional connectivity during emotional processing. A connectivity approach examining connections between brain regions, rather than regional activations, is important to capture the dynamic, complex interactions that mediate behavior. Past studies have used psychophysiological interaction (PPI) analyses to document abnormalities in functional connectivity in BD vs. healthy volunteers (HV) during unmasked face emotion processing. Indeed, these studies do document disrupted functional connectivity between amygdala and prefrontal cortex (PFC). Specifically, aberrant amgydala-ventromedial PFC (vmPFC) connectivity was found across both explicit (Vizueta et al., 2012) and implict (Ladouceur et al., 2011) face paradigms, while aberrant amygdala-ventrolateral PFC (vlPFC; Foland et al., 2008; Vizueta et al., 2012) and amygdala-dorsolateral PFC (dlPFC; Vizueta et al., 2012) connectivities were found during explict face paradigms. Disrupted amygdala-PFC connectivity has been similarly reported in patients with BD during resting state (Torrisi et al., 2013). Although a prior study investigated functional connectivity during an implicit face paradigm (i.e., gender labeling of faces; Ladouceur et al., 2011), no functional connectivity study has used *masked* faces. Thus, the current study is the first one to examine functional connectivity during early, rapid, automatic processing of masked faces in BD patients.

With regard to regional activation during *unmasked* face processing, studies also suggest PFC hypoactivation and limbic hyperactivation in BD across explicit and implicit paradigms (for reviews and meta-analyses, see Blond et al., 2012, Chen et al., 2011, Delvecchio et al., 2012, Houenou et al., 2011, Kupferschmidt and Zakzanis, 2011 and Strakowski et al., 2012). However, only two studies investigated rapid, automatic processing of *masked* faces (presented for ≤33 ms) in BD patients, one in youth (Thomas et al., 2014) and the other in adults (Grotegerd et al., 2014). Thomas et al. (2014) reported hyperactivation in the precentral gyrus, superior temporal gyrus, and medial frontal gyrus in BD youth relative to HV across both masked and unmasked faces, but activation in the middle occipital gyrus varied with awareness level. Grotegerd et al. (2014) found that BD adults, relative to HV, exhibited amygdala hypoactivation to masked sad faces. Grotegerd et al.'s (2010) study used masked faces (no unmasked faces), only probed amygdala activation, and did not examine functional connectivity.

The goal of this study was to compare functional connectivity and regional activation in adults with BD and HV during rapid, automatic vs. explicit processing of emotional faces. Thus, we incorporated both masked and unmasked faces in a single paradigm; investigated functional connectivity, given the importance of understanding connections between brain regions; and conducted a whole-brain analysis and a region of interest (ROI) analysis on the amygdala, an important region for automatic emotional processing (Killgore et al., 2014; Rauch et al., 2000; Whalen et al., 1998). Based on previous research in BD, we hypothesized that BD patients would show disturbed functional connectivity between amygdala and PFC, particularly vlPFC (Foland et al., 2008; Vizueta et al., 2012), vmPFC (Ladouceur et al., 2011; Vizueta et al., 2012) and dlPFC (Vizueta et al., 2012), as these frontal-limbic networks are thought to subserve explicit, elaborative as well as implicit, automatic emotional processing (Phillips et al., 2008). In addition, we hypothesized that BD patients, relative to HV, would demonstrate abnormalities in amygdala, PFC, and occipito-temporal visual cortical activation (Blond et al., 2012; Chen et al., 2011; Delvecchio et al., 2012; Grotegerd et al., 2014; Houenou et al., 2011; Kupferschmidt and Zakzanis, 2011; Lichev et al., 2015; Strakowski et al., 2012; Suslow et al., 2009). The precise nature of neural dysfunction may vary with awareness level (Thomas et al., 2014) or emotions (Thomas et al., 2014). For example, BD patients, relative to HV, may show greater activation to masked vs. unmasked faces (Thomas et al., 2014) and greater activation to angry or happy faces vs. other faces in these regions (Phillips and Vieta, 2007; Thomas et al., 2014).

2. Methods

2.1. Participants

Fourteen adults with BD and 14 HV (Mean age=34.64 years, *SD*=10.2 years) participated in this Institutional Review Board-approved study at the National Institute of Mental Health (NIMH). Written informed consent was obtained from all participants. Adults with BD were recruited through advertisements to support groups, professional meetings, and psychiatrists. HV were drawn from the community through advertisements.

The Structural Clinical Interview for DSM-IV-TR Axis I Disorders – Patient Edition (SCID-I/P; n=11 BD and 14 HV) (First et al., 2002) or the Diagnostic Interview for Genetic Studies (DIGS; n=3 BD) (Nurnberger et al., 1994) was used to determine diagnostic status for patients and controls. The Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD; Williams, 1988) and the Young Mania Rating Scale (YMRS; Young et al., 1978) were used to evaluate mood state in BD patients. Sample characteristics, including mood states and comorbidities, are described in Table 1.

HV were medication-free, and had no lifetime psychiatric diagnoses and no first-degree relatives with mood disorders. Exclusion criteria for all participants included: IQ < 70, history of head trauma, unstable medical illness, neurological disorder, pervasive developmental disorder, active psychotic symptoms, or substance abuse/dependence within the past 3 months.

2.2. fMRI paradigm

Participants completed an affective priming task (Tseng et al., 2016) during fMRI data acquisition. The task consisted of four runs: two for the aware condition (with unmasked faces) and two for the non-aware condition (with masked faces). The runs were interleaved, i.e., alternating between aware and non-aware conditions, and the order of the runs was counterbalanced across participants. In the *aware* condition, subjects saw a fixation cross (1250–1750 ms, average 1500 ms), followed by a face or blank oval (187 ms), and then an abstract shape (3000 ms; see Fig. 1). In the *non-aware* condition, subjects saw a fixation cross (1250–1750 ms, average 1500 ms), followed by a face or blank oval (17 ms), a scrambled face mask (170 ms), and finally an abstract shape (3000 ms; Fig. 1). Eprime was used to present the stimuli. The stimulus onset and duration were recorded in Eprime and checked to ensure the exact timing and duration were good. The facial stimuli were taken from the NimStim set of facial expressions (Tottenham et al., 2009). The abstract shapes were taken from a pool of 101 exemplars. The shapes were not the same in each run; they were randomized without repeat. Because of randomization, there should be no associations between shapes and face stimuli. Each event was 3187 ms long. To test whether behavioral responding was influenced by the emotional primes and ensure participants were attending, in both the aware and non-aware conditions, participants indicated on a scale from 1 (did not like) to 5 (liked a lot) how much they liked the abstract shape presented after the masked or unmasked face (Fig. 1). The face stimuli, angry, happy, neutral, or "no face" (blank oval), were presented randomly; there were 36 trials for each stimulus under each awareness condition. The duration of the task was approximately 28 min. Prior to scanning, outside the scanner on a desktop computer, participants completed a practice run of 8 trials for each awareness condition, using faces not presented during scanning.