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Neural circuitry of masked emotional face processing in youth with bipolar disorder, severe mood dysregulation, and healthy volunteers

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ABSTRACT

Youth with bipolar disorder (BD) and those with severe, non-episodic irritability (severe mood dysregulation, SMD) show face-emotion labeling deficits. These groups differ from healthy volunteers (HV) in neural responses to emotional faces. It is unknown whether awareness is required to elicit these differences. We compared activation in BD ($N = 20$), SMD ($N = 18$), and HV ($N = 22$) during "Aware" and "Non-aware" priming of shapes by emotional faces. Subjects rated how much they liked the shape. In aware, a face (angry, fearful, happy, neutral, blank oval) appeared (187 ms) before the shape. In non-aware, a face appeared (17 ms), followed by a mask (170 ms), and shape. A Diagnosis-by-Awareness-by-Emotion ANOVA was not significant. There were significant Diagnosis-by-Awareness interactions in occipital regions. BD and SMD showed increased activity for non-aware vs. aware; HV showed the reverse pattern. When subjects viewed angry or neutral faces, there were Emotion-by-Diagnosis interactions in face-emotion processing regions, including the L precentral gyrus, R posterior cingulate, R superior temporal gyrus, R middle occipital gyrus, and L medial frontal gyrus. Regardless of awareness, BD and SMD differ in activation patterns from HV and each other in multiple brain regions, suggesting that BD and SMD are distinct developmental mood disorders.

1. Introduction

In this study we compared neural activation in youth with bipolar disorder (BD), those with severe, non-episodic irritability (severe mood dysregulation, or SMD), and healthy volunteers (HV) while they completed a paradigm involving processing of faces presented above or below the threshold for awareness. The comparison between SMD and BD is motivated by the recent increase in the prevalence of pediatric BD diagnosed in clinical settings (Blader

Abbreviations: BD, bipolar disorder; SMD, severe mood dysregulation; ADHD, attention deficit hyperactivity disorder; HV, healthy volunteer.

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and Carlson, 2007; Moreno et al., 2007). This increase was concurrent with the contention in the child psychiatry literature that BD manifests in youth as severe, non-episodic irritability, rather than with discrete episodes of mania and depression (Biederman et al., 2000). Thus, the SMD phenotype was defined to facilitate research on youth with this controversial phenotype (Leibenluft, 2011). Studies of family history and longitudinal course suggest that BD and SMD are dissociable (Brotman et al., 2006, 2007; Stringaris et al., 2010). However, both SMD and BD youth, but not those with other psychiatric illnesses, show perturbed face-emotion labeling ability (McClure et al., 2003, 2005; Guyer et al., 2007; Schenkel et al., 2007; Rich et al., 2008), although evidence suggests that the neural activity mediating face processing may differ between SMD and BD (Brotman et al., 2010; Thomas et al., 2012, 2013).

Emotional facial expressions can influence responding even in research participants who remain unaware of a face's emotional content (Ohman and Mineka, 2001). Therefore, it is important to test whether neutral activation in response to face emotion differs among SMD, BD, and HV when they are unaware of the emotional face stimulus. Potentially, aberrant automatic (non-aware) processing of emotional stimuli may contribute to symptoms of emotional problems in both BD and SMD. One way to test this hypothesis is through the use of affective priming, which incorporates a technique called backwards masking. In backwards masking, a prime stimulus is presented too quickly to reach awareness, followed by a target stimulus (mask) that is presented long enough to be identified. In affective priming paradigms, the prime consists of an emotional stimulus, typically an emotional face, followed by a mask stimulus that participants are asked to evaluate. Research with affective priming demonstrates that a brief exposure to an emotional-face prime can influence judgments of affectively neutral stimuli that are presented subsequently (Murphy and Zajonc, 1993; Winkielman et al., 1997).

In healthy adults, some evidence suggests that affective priming paradigms can activate a "fast-route" that bypasses conscious perception (LeDoux, 1996) and includes areas such as the amygdala, fusiform gyrus, hippocampus, anterior cingulate, insula, and primary visual cortex (Morris et al., 1998; Whalen et al., 1998; Nomura et al., 2004; Garolera et al., 2007; Kim et al., 2010; Brooks et al., 2012). The subject's inability to identify a prime is thought to result from effects of the target stimulus on the ventral visual stream, which includes the lateral occipital cortex and regions in the lingual and fusiform gyri, regions that mediate object recognition (Ungerleider and Mishkin, 1982; Hasson et al., 2002). Indeed, lateral occipital cortex activation correlates positively with the strength of masking effects in healthy adults (Green et al., 2005).

Compared with healthy subjects, adults with mood and anxiety disorders have increased amygdala activation to masked emotional faces compared with healthy volunteers (Rauch et al., 2000; Sheline et al., 2001; Armony et al., 2005; Dannlowski et al., 2006a,b, 2008; Li et al., 2008; Tsunoda et al., 2008; Suslow et al., 2010). For example, there is increased amygdala activation to masked emotional faces in adults with unipolar depression compared to their healthy counterparts (Suslow et al., 2010; Victor et al., 2012). In addition, similar studies report that when compared to healthy subjects, patients with schizophrenia have decreased ventrolateral occipital activation when unaware of the mask stimulus (Green et al., 2009).

There have been a few backwards masking paradigms involving youth (Pine et al., 2001; Hall et al., 2007; Killgore and Yurgelun-Todd, 2007; Monk et al., 2008; Viding et al., 2012). However, these studies did not compare awareness states as we do, and to date no fMRI affective priming study includes youth with any mood disorder. Here, we use such a paradigm to compare BOLD activation patterns in pediatric SMD, BD, and HV.

Our experiment used face stimuli presented in unmasked/aware (187 ms) and masked/non-aware (17 ms) conditions. In both conditions the face was followed by an abstract shape, and subjects rated how much they liked the shape. Face emotions were anger, fear, happy, neutral and a blank oval (Suslow et al., 2006). The blank oval was included to disambiguate responses to face emotions from responses to faces per se, and because youth with BD and SMD rate neutral faces more negatively than do HV (Rich et al., 2006; Brotman et al., 2010).

To date, three neuroimaging studies directly compare amygdala activity in BD and SMD during face emotion processing (Brotman et al., 2010; Thomas et al., 2012, 2013). Because these studies used different paradigms, it is difficult to compare their results directly. Brotman et al. (2010) found that SMD, compared to BD and HV youth, exhibited amygdala hypo-activation during explicit processing of neutral faces. However, both Thomas et al. (2012, 2013) found that BD and SMD had similar amygdala dysfunction vs. HV, with Thomas et al. (2012) reporting less modulation of amygdala activity in BD and SMD compared to HV, and Thomas et al. (2013) finding overall hyperactivity in the amygdala to emotional faces in both BD and SMD. Due to these varying results from differing experimental paradigms, we were unable to posit specific hypotheses about how amygdala activity might differ between BD and SMD. However, based on the aforementioned research with adult unipolar depression demonstrating increased amygdala activity to masked emotional faces, as well as previous work with pediatric BD and SMD (Brotman et al., 2010; Thomas et al., 2012), we hypothesized that amygdala activity would be greater for the masked faces in the mood-disordered BD and SMD groups vs. HV.

Additionally, we hypothesized that there would be awareness-modulated group differences in ventrolateral occipital activation based on work in adults with schizophrenia (Green et al., 2009). Possible group differences between BD, SMD, and HV based on awareness would add to data demonstrating that BD and SMD differ clinically, neuropsychologically, and pathophysiologically. These differences suggest that SMD and BD may be manifestations of differing developmental pathologies along a mood disorders spectrum. Comparisons of both groups with healthy age-matched controls will help disentangle possible normative developmental effects vs. the presence of a mood disorder.