Journal of Psychiatric Research 45 (2011) 1283–1294

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Different neural pathways to negative affect in youth with pediatric bipolar disorder and severe mood dysregulation

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ARTICLE INFO

Article history:
Received 13 December 2010
Received in revised form
8 April 2011
Accepted 14 April 2011

Keywords:
Bipolar disorder
Pediatric
Mood dysregulation
Irritability
Frustration
Magnetoencephalography

ABSTRACT

Questions persist regarding the presentation of bipolar disorder (BD) in youth and the nosological significance of irritability. Of particular interest is whether severe mood dysregulation (SMD), characterized by severe non-episodic irritability, hyper-arousal, and hyper-reactivity to negative emotional stimuli, is a developmental presentation of pediatric BD and, therefore, whether the two conditions are pathophysiologically similar. We administered the affective Posner paradigm, an attentional task with a condition involving blocked goal attainment via rigged feedback. The sample included 60 youth (20 BD, 20 SMD, and 20 controls) ages 8–17. Magnetoencephalography (MEG) examined neuronal activity (4–50 Hz) following negative versus positive feedback. We also examined reaction time (RT), response accuracy, and self-reported affect. Both BD and SMD youth reported being less happy than controls during the rigged condition. Also, SMD youth reported greater arousal following negative feedback than both BD and controls, and they responded to negative feedback with significantly greater activation of the anterior cingulate cortex (ACC) and medial frontal gyrus (MFG) than controls. Compared to SMD and controls, BD youth displayed greater superior frontal gyrus (SFG) activation and decreased insula activation following negative feedback. Data suggest a greater negative affective response to blocked goal attainment in SMD versus BD and control youth. This occurs in tandem with hyperactivation of medial frontal regions in SMD youth, while BD youth show dysfunction in the SFG and insula. Data add to a growing empirical base that differentiates pediatric BD and SMD and begin to elucidate potential neural mechanisms of irritability.

1. Objectives

The past decade has witnessed a significant rise in the rate at which the diagnosis of bipolar disorder (BD) is assigned to youth. Studies of diagnoses from outpatient visits (Moreno et al., 2007) and at discharge from psychiatric hospitals (Blader and Carlson, 2007) document dramatic increases in the rate at which the diagnosis of BD is being assigned to youth. Although empirical data are lacking, researchers have hypothesized that one possible cause for this increase may be the assignment of the BD diagnosis to youth who have severe affective and behavioral dysregulation but lack the distinct manic episodes required to meet DSM-IV criteria for BD (Donovan et al., 2003; Harris, 2005; Moreno et al., 2007; Zimmerman et al., 2008). This phenotype has been operationalized in the syndrome of severe mood dysregulation (SMD) (Leibenluft et al., 2003). SMD is defined as 1) non-episodic, severe irritability and anger; 2) hyper-arousal symptoms common to both BD and Attention Deficit Hyperactivity Disorder (ADHD); and, 3) extreme hyper-reactivity to negative emotional stimuli which, while similar to the "loses temper" criterion of Oppositional Defiant Disorder (ODD) (McMahon and Wells, 1998), is operationalized more precisely and requires greater severity in the SMD classification. SMD youth are an important research sample because while most SMD youth meet criteria for ADHD and/or ODD, neither of these diagnoses requires extreme irritability, which is operationalized clearly in SMD. In addition, although SMD youth have many symptoms which overlap with BD, they fail to meet DSM-IV criteria for mania because SMD irritability is non-episodic. Further, SMD youth lack a history of episodic euphoric/grandiose mood lasting more than one day (Leibenluft et al., 2003).

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doi:10.1016/j.jpsychires.2011.04.006

Irritability is a mood state characterized by a low threshold for frustration, where frustration is the affective response to blocked goal attainment. This typically results from the failure to receive an expected reward or outcome, often in conjunction with rigged feedback (Moadab et al., 2010; Siegrist et al., 2005; Abler et al., 2005; Yu et al., 2010). Irritability is, in many ways, ubiquitous in childhood psychopathology. It is a diagnostic criterion for major depressive disorder (MDD) and generalized anxiety disorder (GAD), and is often seen in children with other anxiety disorders, ADHD, ODD, and pervasive developmental disorders (PDD).

Clarifying the role of irritability in the diagnosis and pathophysiology of pediatric BD, and in the differentiation of pediatric BD and SMD, has garnered significant interest. Irritability is prevalent in BD (Geller et al., 1998) and, by definition, in SMD as well. Although irritability is impairing in BD (Carlson et al., 2003), data suggest that SMD youth are significantly more irritable than BD youth (Stringaris et al., 2010). Further, the presentation of irritability differs between the syndromes. The irritability of SMD is non-episodic. In contrast, to be diagnostic of mania seen in BD, irritability must present in a distinct episode. Specifically, if irritability is to be the "index" affect for a manic episode, it has to either have the same onset as the "B" criteria of mania or, if it pre-dates the onset of the "B" criteria, it has to worsen significantly at the time that the "B" criteria occur. Thus, irritability that is chronically present would not be diagnostic of a manic episode because it would not satisfy the DSM-IV requirement that the affect present during the episode represent a "distinct" period of abnormal mood. Results of two longitudinal epidemiological studies speak to the potential importance of this difference in presentation: youth with non-episodic irritability are at risk for unipolar depression and anxiety, rather than BD, by adulthood (Brotman et al., 2006; Stringaris et al., in press).

Additional comparisons of SMD and BD youth suggest divergent neurophysiological mechanisms mediating the response to blocked goal attainment in these two populations. We have compared the neural mechanisms mediating response to blocked goal attainment in BD and SMD youth using the affective Posner task, which uses rigged feedback that informs the subject of lost monetary reward, to a standard task of orienting attention. In our first comparison of BD and SMD youth using the affective Posner task (Rich et al., 2007) we found that in the rigged feedback context, both BD and SMD youth had slower reaction times than controls (BD also were slower than SMD), and both patient samples had more negative affective responses than controls. However, the patient samples differed in their psychophysiological deficits, as measured by ERP's, in response to the attention-cuing stimuli. Whereas BD subjects displayed lower parietal P3 amplitude than SMD or controls in the emotional rigged feedback condition only, SMD youth had lower frontal, temporal, and central N1 and central P1 amplitude than BD and controls in both emotional and non-emotional contexts. These results suggest that in BD youth, deficits in executive attention are seen specifically in the rigged feedback context, whereas SMD youth display deficits in the initial stages of attention, regardless of the emotional nature of the context. Overall, these results indicate that the affective and behavioral deficits in BD and SMD youth may have divergent attention- and emotion-driven neural perturbations.

The current study extends our prior ERP research by using magnetoencephalography (MEG) to compare SMD, BD, and controls to attain a more spatially-detailed comparison of the neural mechanisms engaged during blocked goal attainment. We previously used MEG and the affective Posner paradigm to compare BD and control subjects on theta band (4–8 Hz) power, given its role in attention to emotional stimuli (Aftanas et al., 2003; Aftanas et al., 2001). We found that, in the rigged feedback context, BD youth displayed greater theta power than controls in the anterior cingulate cortex (ACC) and parietal lobe in response to negative feedback (Rich et al., 2010b).

Here we compare SMD subjects to the previously studied BD and control subjects. We examined a broad band of MEG power (4–50 Hz), which is comparable to the approach used in our prior ERP study. Also, we examined neuronal activity in response to the emotional stimuli (i.e. negative and positive feedback) rather than to the attentional target, in order to better understand the neural correlates of processing rewarding and punishing affective stimuli. We predicted attenuated ACC activation in SMD youth compared to BD and control youth because our prior MEG study found heightened ACC activation in BD youth compared to controls (Rich et al., 2010b), while our prior ERP study found N1 amplitude deficits in SMD youth (Rich et al., 2007), and studies implicate the ACC in generating N1 (Esposito et al., 2009; Mulert et al., 2008).

2. Materials and methods

2.1. Participants

Sixty youth (20 BD, 20 SMD, 20 control) ages 8–17 years enrolled in an IRB-approved study at the National Institute of Mental Health (NIMH). Subjects were recruited from across the United States through newspaper and Internet advertisements, flyers distributed at professional conferences, and letters sent to child psychiatrists nationwide. Subjects and a guardian provided written informed assent/consent. While BD and control data are published (Rich et al., 2010b), the data on SMD youth have not been presented previously.

To identify SMD and BD, we used the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), a semi-structured diagnostic interview administered to parents and children separately by graduate level clinicians with established reliability (i.e. kappa $\geq$ .9, by blinded review of taped evaluations).

All BD subjects met DSM-IV criteria for BD, with the requirement of at least one full duration hypomanic ($\geq$4 days) or manic ($\geq$7 days) episode, defined by an abnormally elevated or expansive mood and/or grandiosity (Leibenluft et al., 2003). Comorbid diagnoses, also assessed using the K-SADS, required impairment during euthymia.

SMD classification inclusion criteria were non-episodic abnormal mood (anger or sadness), present at least half of the day most days, and of sufficient severity to be noticeable to others, over-reactivity to negative emotional stimuli (e.g. explosive tantrums) at least three times weekly, and hyper-arousal symptoms (including at least three of the following: insomnia, intrusiveness, pressured speech, flight of ideas/racing thoughts, distractibility, psychomotor agitation) (Leibenluft et al., 2003). Symptoms had to begin prior to age 12, and be present for at least one year without remission for longer than two months. Symptoms had to cause severe impairment in one setting (home, school, peers), and at least mild impairment in another. Euphoric mood or distinct episodes lasting $\geq$1 day were exclusionary (Leibenluft et al., 2003).

A K-SADS supplementary module assessed the presence and severity of eight symptoms to determine if children met criteria for the SMD classification: irritable mood, insomnia, racing thoughts, distractibility, physical restlessness, intrusiveness, pressured speech, and markedly excessive reactivity in response to a negative or frustrating emotional stimulus. For all, in addition to assessing the intensity of and impairment associated with these symptoms, questions pertaining to frequency and course allowed clinicians to determine if the symptoms presented in a chronic, non-episodic manner, consistent with the SMD classification. Differentiation of SMD from BD had excellent reliability (i.e. kappa $\geq$ .9, by blinded review of randomly selected taped evaluations).