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Aberrant amygdala intrinsic functional connectivity distinguishes youths with bipolar disorder from those with severe mood dysregulation

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ABSTRACT

It remains unclear the degree to which youths with episodic mania (bipolar disorder; BD) vs. those with chronic, severe irritability (severe mood dysregulation, SMD) should be placed in similar or distinct diagnostic groups. Addressing this clinically meaningful question requires greater understanding of the neural alterations underlying both disorders. We evaluated resting state functional magnetic resonance imaging data of 53 youths (14 BD, 20 healthy volunteers (HV), and 19 SMD, ages 9–18.5 years). Seed regions of interest were the bilateral basolateral, superficial and centromedial amygdala, defined using the Juelich probabilistic atlas. We found a significant between-group difference in functional connectivity between the left basolateral amygdala and the medial aspect of the left frontal pole plus the posterior cingulate/precuneus. This finding was driven by hyperconnectivity among BD vs. HV or SMD youths. As with earlier data, these findings suggest that the pathophysiology of BD and SMD may differ.

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1. Introduction

Pathologic irritability in youths is impairing, common, and associated with adverse outcomes (Leibenluft and Stoddard, 2013). Clinicians and researchers have struggled to determine if severe, chronic irritability without episodic mania is a developmental phenotype of bipolar disorder (BD). To address this question, we phenomenologically and pathophysiologically compared youths with distinct episodes of mania ("narrow phenotype BD" [NPBD]) vs. those with chronic, functionally impairing irritability who meet criteria for "severe mood dysregulation" (SMD) (Leibenluft et al., 2003, 2011). Findings documenting differences between SMD and NPBD contributed to the Diagnostic and Statistical Manual 5th edition (DSM-5)'s new diagnosis Disruptive Mood Dysregulation Disorder (American Psychiatric Association, 2013). Still, further work is needed to advance what is known about the neural pathophysiology of chronic irritability vs. episodic mania. Here, we compare their neural functional organization by testing amygdala intrinsic functional connectivity (iFC) in NPDB vs. SMD.

Earlier task-dependent functional magnetic resonance imaging (fMRI) studies indicate that both BD and SMD are associated with amygdala dysfunction. Further, studies of explicit face emotion processing show differences between BD and SMD in the nature of that dysfunction (Brotman et al., 2010; Thomas et al., 2012). Measuring amygdala iFC can extend this work by evaluating dysfunction in amygdala-based neural networks. Intrinsic functional connectivity (i.e., the correlation of spontaneous fluctuations in neural activity between brain regions) indexes these regions' organization into networks required for brain operations. Earlier iFC studies suggest that BD may be characterized by amygdala–prefrontal cortex (PFC) dysconnectivity. The strongest evidence is in adults with BD (Anand et al., 2009; Chepenik et al., 2010; Anticevic et al., 2013; Torrisi et al., 2013; Favre et al., 2014). Fewer studies have examined amygdala iFC in pediatric BD. One that used a coordinate-based sphere did not find amygdala abnormalities in euthymic BD youths (Dickstein et al., 2010), while another found abnormal fronto-amygdala iFC in manic youths

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(Wu et al., 2013). No study has evaluated iFC in SMD or DMDD youths. However, youths with ADHD and high emotional lability clinically resemble those with SMD (Merwood et al., 2014), and one study of youths with ADHD found that emotional lability was positively associated with amygdala–medial PFC iFC (Hulvershorn et al., 2014).

Here, we provide the first iFC study evaluating amygdala connectivity with the whole brain among BD, SMD, and HV youths. We hypothesized that BD and SMD youths would differ in amygdala iFC, particularly within the PFC, based on the above-mentioned studies.

2. Methods

2.1. Participants

This Institutional Review Board-approved study was conducted at the National Institute of Mental Health (NIMH). Participants and their parents gave written informed assent/consent before study participation.

Sixty-four SMD, BD, and HV youths (9–18 years) completed a resting state fMRI scan. Of the 64 scans, one SMD participant and one HV participant were excluded due to extreme motion artifact, and one SMD participant was excluded for improper field of view placement. Of the remaining 61 individuals that underwent image processing, two SMD participants were excluded for anatomic registration failure and six for regression failure due to motion (two BD, one HV, and three SMD). The final analysis included 53 participants (14 BD, 20 HV, and 19 SMD; Table 1).

2.2. Measures

Psychiatric diagnoses were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (KSADS-PL) administered by master's or doctoral-level clinicians trained to high reliability ($\kappa > 0.9$). Diagnoses were confirmed in case conference with a senior psychiatrist (Kaufman et al., 1997).

BD inclusion criteria were meeting full DSM-IV (American Psychiatric Association, 2000) criteria for BD I or II. All BD youths met the definition of Leibenluft et al. for NPBD, which includes at least one $\geq$7-day manic or 4–7 days hypomanic episode involving euphoria and/or grandiosity plus three B symptoms (Leibenluft et al., 2003). The rationale for these criteria was to ensure universal agreement that these children had BD. Youths with brief ($<$4 days) episodes of hypomania and youths with irritable-only mania without grandiosity would not be included in this study.

SMD inclusion criteria were abnormal baseline mood, hyper-reactivity to negative emotional stimuli (i.e., developmentally inappropriate outbursts at least 3 times/week), and hyperarousal ($\geq$3 of insomnia, intrusiveness, pressured speech, flight of ideas/racing thoughts, distractibility, psychomotor agitation) (Leibenluft et al., 2003). SMD symptoms must begin before age 12, occur for $\geq$1 year without remission exceeding 2 months, and cause impairment in at least two of three settings (home, school, or with peers). Euphoric mood or distinct (hypo)manic episodes lasting $>$1 day were exclusionary for SMD.

HV inclusion criteria were the absence of Axis I psychopathology, first degree relatives with a mood disorder, or psychotropic medication use.

Exclusion criteria for all groups were chronic or active medical conditions, autism spectrum disorder, substance use within the last 2 months, head trauma, and full-scale IQ $<$70, measured using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) or the Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2004).

Mood and anxiety symptoms were assessed within 3 days of scanning in patients. BD participants' manic symptoms were measured by the Young Mania Rating Scale (YMRS) (Young et al., 1978). The YMRS may be used with an adolescent population (Youngstrom et al., 2002), and symptoms were rated by clinicians using information from separate interviews of both child and parent. Among BD and SMD participants, depression was measured with the Children's Depression Rating Scale (CDRS) (Poznanski et al., 1979), anxiety was measured with the Pediatric Anxiety Rating Scale (PARS) (The Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002), and 6-month severity was measured with the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) (Table 1).

Table 1
Participant characteristics[a].

	HV $n=20$	SMD $n=19$	BD[b] $n=14$	Comparison
Sex, *n* (%) female	11 (55)	6 (32)	3 (21)	$\chi^2=4.43$, $p=0.11$
Age, years, mean (S.D.)	14.3 (2.3)	13.9 (2.5)	14.6 (2.5)	$F(2,50)=0.36$, $p=0.70$
IQ[c], mean (S.D.)	108.4 (10.4)	107.2 (12.1)	103.3 (12.7)	$F(2,44)=0.73$, $p=0.49$
YMRS[c] score, mean (S.D.)			8.5 (6.6)	
CDRS[c] score, mean (S.D.)		25.2 (4.2)	27.5 (9.4)	$t(15.4)=0.82$, $p=0.42$
PARS[c] score, mean (S.D.)		12.5 (5.7)	13.3 (5.2)	$t(25.2)=0.37$, $p=0.71$
CGAS[c] score, mean (S.D.)		51.2 (7.9)	50.0 (9.3)	$t(23.1)=0.38$, $p=0.71$
Mood state[d], *n* (%)				
Manic			0	
Hypomanic			2	
Mixed			1	
Depressed		0	1	$\chi^2=0.04$, $p=0.85$
Euthymic		19	9	$\chi^2=4.16$, $p=0.04$
Lifetime KSADS diagnoses, *n* (%)				
ADHD		16 (84)	11 (79)	$\chi^2=0$, $p=1$
ODD or CD		16 (84)	7 (50)	$\chi^2=2.99$, $p=0.08$
Any anxiety		17 (89)	12 (86)	$\chi^2=0$, $p=1$
GAD		15 (79)	8 (57)	$\chi^2=0.93$, $p=0.34$
SAD		11 (58)	7 (50)	$\chi^2=0.01$, $p=0.92$
SoPh		3 (16)	5 (36)	$\chi^2=0.83$, $p=0.36$
Medication[e], *n* (%)				
None	20 (100)	7 (37)	4 (29)	$\chi^2=0.02$, $p=0.90$
Antipsychotic		6 (32)	7 (50)	$\chi^2=0.50$, $p=0.48$
Lithium		1 (5)	4 (29)	$\chi^2=1.83$, $p=0.18$
Antiepileptic		4 (21)	5 (36)	$\chi^2=0.29$, $p=0.59$
Antidepressant		7 (37)	2 (14)	$\chi^2=1.08$, $p=0.30$
Stimulant		4 (21)	4 (29)	$\chi^2=0.01$, $p=0.93$

[a] HV=healthy control; SMD=severe mood dysregulation; BD=bipolar disorder; YMSR= Young Mania Rating Scale; CDRS=Children's Depression Rating Scale; CGAS=Children's Global Assessment Scale; ADHD=attention deficit/hyperactivity disorder; ODD=oppositional defiant disorder; CD=conduct disorder; SAD=separation anxiety disorder; GAD=generalized anxiety disorder; and SoPh=social phobia.

[b] Eleven BD youths met criteria for BD I and three met for BD II.

[c] IQ was missing for six participants (one BD, three HV, and two SMD). YMRS, PARS, CDRS, and medication data missing for one BD participant. CGAS data missing for another BD participant and SMD participant. PARS data missing for a third BD participant and another SMD participant.

[d] Mood state was determined by YMRS and CDRS score. For SMD and BD depressed state limits were YMRS $\leq$12 and CDRS $\geq$40. For BD only, hypomanic limits were YMRS $>$12 but $<$26 and CDRS $<$40, mania limits were YMRS $\geq$26 and CDRS $<$40, and mixed state limits were YMRS $>$12 and CDRS $\geq$40.

[e] All medication comparisons are between BD and SMD only.