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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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Disclosures

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Keywords

Irritability; Functional connectivity; Magnetic resonance imaging; Bipolar disorder; Child

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; Leibenluft, 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 NPBD 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 vs. 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 (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 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 (2 BD, 1 HV, 3 SMD). The final analysis included 53 participants (14 BD, 20 HV, 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 7-day manic or 4- to 7-day 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 (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 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).

2.3. Image acquisition

MR images were acquired on three General Electric 3.0 Tesla scanners (Table 2). Resting state fMRI scans were acquired while participants passively viewed a fixation cross. Blood oxygen-level dependent (BOLD) signal was measured by echoplanar imaging (EPI) with the same parameters across scanners: flip angle=90°, echo time=30 ms, repetition time=2.0 s, 180 volumes, acquisition time=6 min, field of view=192 mm, and acquisition voxel size=3×3×4 mm. For anatomic registration and normalization, high resolution T1-weighted MPRAGE images were collected with some variation by scanner. For scanner 1: flip angle=7°, minimum full echo time, inversion time=425 ms, acquisition voxel size=1 mm isotropic; for scanners 2 and 3: flip angle=6°, minimum full echo time, inversion time=725 ms, acquisition voxel size=0.86×1.15×1.20mm.

2.4. Image processing

All images were processed using the Analysis of Functional Neuroimages (AFNI) resting state image processing stream (Jo et al., 2013) to minimize the effect of motion, physiological, and hardware noise. Motion and global correlation did not differ significantly among groups (Table 2).

EP images were processed by excising the first four volumes, limiting each voxel's BOLD signal to 4 standard deviations from the mean trend of its time series, correcting for slice timing, registering by affine transformation to a Montreal Neurological Institute (MNI) template, and smoothing using a 4-mm full-width at half-maximum Gaussian kernel. All images were visually inspected for acquisition artifact and registration. Processed images were then entered into nuisance regression with the following parameters: a cubic detrending polynomial, 12 motion parameters, bandpass filter parameters with limits of 0.01 and 0.1 Hz, and local white matter signal parameters derived from the ANATICOR method (Jo et al., 2013). Any EPI volume with a Euclidean mean of 0.3-mm shift from its preceding volume was censored from regression along with its preceding volume. Therefore, subject-level exclusion for motion was based on the 0.3-mm censoring, i.e., too many motion-censored volumes led to nuisance regression failure due to insufficient degrees of freedom. Residuals from this nuisance regression represented neural BOLD signal for further analysis.

2.5. Region of interest (ROI) selection

The amygdala is a heterogeneous group of nuclei with distinct functions. For the purposes of iFC analyses, Roy et al. (2009) demonstrated that it is possible to generate three amygdala ROI subdivisions from a probabilistic cytoarchitectonic-based atlas in MNI space (Amunts et al., 2005). They found that a 50% probability threshold can identify basolateral, superficial, and centromedial ROIs that each generates an iFC network consistent with each subdivision's functional connectivity as suggested by other research modalities in animals and humans.

Following Roy et al. (2009, 2013), we created amygdala ROIs for the basolateral, superficial, and centromedial amygdala subdivisions. First, we exported the amygdala subdivision probabilistic maps from FSL's Juelich cytoarchitectonic map in MNI 152 2-mm space (Amunts et al., 2005). We thresholded each map at 50% and performed pairwise comparisons. Where probability maps overlapped, each voxel was assigned to its most likely subdivision. Rare voxels that had an equally high probability of belonging to two subdivisions were excluded (Fig. 1). Resultant probability maps were converted to binary ROI masks.

2.6. Single-subject connectivity maps

In AFNI, amygdala ROIs were resampled to a participant's EPI dimensions and intersected with the participant's EPI mask. We calculated the mean BOLD timeseries within each amygdala ROI and then used 3dTCorr1D to generate a voxel-wise Pearson's correlation map for each ROI. We used Fisher's r to z transformation to prepare the maps for group analysis.

2.7. Group analysis

Group-level analysis of each connectivity map was done by analysis of covariance (ANCOVA) using 3dMVM with a main factor of group (HV, SMD, and BD) and covariates sex (male or female) and scanner (1, 2, or 3). The group-level formula was Fisher's z (Connectivity) = Group + Sex + Scanner + Intercept + Error.

Results were thresholded voxel-wise at $p < 0.005$. Cluster correction was used to control for multiple tests across whole brain gray matter via 3dClustSim. To account for six seed analyses, the cluster correction alpha level was Bonferroni-corrected to 0.008 ($< 0.05/6$), yielding a threshold of 44 voxels (1188 μl). For each cluster that differed between the groups, a mean Fisher's z was calculated at the single subject level for *post hoc* analysis. All *post hoc* and demographic analyses were conducted using analyses of variance (ANOVAs) and proportion tests as appropriate in R, version 3.0.2 (R Core Team, 2012).

3. Results

Table 1 shows participant characteristics. Of note, all but one of the SMD participants met criteria for DMDD; that one did not because his age of onset was 10 years old. Sex was included as a covariate in the group analysis (p for group difference = 0.11).

The groups differed in iFC (mean Fisher's z) between the left basolateral amygdala ROI (LBL) and two cortical clusters. One was a posterior cluster with a peak difference in the left posterior cingulate (Fig. 2; Supplemental Image 1) extending contralaterally into the right posterior cingulate and posteriorly and dorsally into the left precuneus. LBL iFC to this cluster differed among groups ($F(2,50) = 11.53$, $p = 0.00008$), with $BD > HV$, $BD > SMD$, and $HV = SMD$ (Holm-Bonferroni corrected t -tests; p 's = 0.002, <0.001, and 0.21, respectively).

The other, anterior cluster had a peak LBL iFC group difference in the left frontal pole (Fig. 3; Supplemental Image 1) primarily in the medial superior frontal gyrus. iFC in this cluster differed among groups ($F(2,50) = 9.63$, $p = 0.0003$), with $BD > HV$, $BD > SMD$, and $HV = SMD$ (Holm-Bonferroni corrected t -tests; p 's = 0.005, <0.001, and 0.21, respectively; Fig. 3).

When only the nine euthymic BD individuals were included, the group differences in LBL iFC remained significant in the posterior cluster [$F(2,45) = 6.93$, $p = 0.002$, with $BD > HV$ ($p = 0.02$), $BD > SMD$ ($p < 0.002$), and $HV = SMD$ ($p = 0.22$)] and the anterior cluster [$F(2,45) = 6.37$, $p = 0.003$, with $BD > HV$ ($p = 0.02$), $BD > SMD$ ($p < 0.003$), and $HV = SMD$ ($p = 0.23$)]. In BD and SMD, CDRS, PARS, and CGAS scores did not correlate with LBL iFC to either cluster. In ANCOVAs, these measures moderated, but did not account for, the LBL iFC differences between BD and SMD (Supplemental Information 1). Finally, analyses excluding participants by medication class (i.e., taking any antipsychotic, lithium, antiepileptic, antidepressant, or stimulant) confirmed group differences in iFC (p 's = 0.008) and the pattern of pair-wise differences (i.e., $BD > HV$ and $BD > SMD$ [p 's = 0.05])

4. Discussion

Supporting the hypothesis that BD with episodic euphoria differs from severe, chronic irritability pathophysiologically, we found that BD youths differed in basolateral amygdala hyperconnectivity vs. both HV and SMD youths (Cohen's d 's > 1.0). These findings support earlier reports of aberrant fronto-amygdala iFC in BD and pathophysiological differences between BD and SMD.

Our findings are consistent with the broader BD literature implicating functional abnormalities in the amygdala and medial PFC. Specifically, our results align with recent studies finding amygdala hyperconnectivity to the medial PFC in adult BD (Anticevic et al., 2013; Favre et al., 2014). Additionally, including only euthymic individuals supported the hypothesis that fronto-amygdala hyperconnectivity is a trait marker for BD (Anticevic et al., 2013; Torrisi et al., 2013; Favre et al., 2014). In pediatric BD, one study reported abnormal fronto-amygdala iFC in youths during a manic state (Wu et al., 2013). In contrast, Dickstein et al. (2010) did not find altered amygdala iFC in BD youths; however, that study used a spherical seed based on coordinates from an earlier voxel-based morphometry study (Dickstein et al., 2005), whereas our study uses an atlas-derived anatomical seed. We also found amygdala hyperconnectivity in BD to posterior regions associated with the DMN (Greicius et al., 2003). Aberrant iFC between the amygdala and default mode network (DMN) areas, other than the medial PFC, have not been reported in BD, perhaps because most research on amygdala iFC in BD used analyses restricted to the PFC and striatum. Of

note, we did not directly compare DMN connectivity between BD and HV groups in this study.

The functional significance of these findings requires further investigation. The frontal cluster that we identified is largely within the medial aspect of the frontal pole, which is richly connected, functionally and anatomically, with the DMN and areas mediating social-emotional processing, e.g., ventromedial PFC, temporal pole and amygdala (Liu et al., 2013). Aberrant amygdala-DMN connectivity is consistent with the amygdala's role in processing internal stimuli. Since the frontal pole also mediates cognitive flexibility (Koechlin and Hyafil, 2007), future research may assess whether amygdala-frontal pole dysconnectivity mediates the cognitive inflexibility found in pediatric BD (Dickstein et al., 2007a).

We detected differences in iFC only to the basolateral amygdala, which is implicated in threat conditioning (LeDoux, 2014) and emotional encoding (McGaugh, 2004). In BD youths, amygdala volumetric abnormalities have been localized to the basolateral group (Kelley et al., 2013). We simultaneously tested group differences in connectivity to both the RBL and LBL ROIs using multivariate analysis of variance in 3dMVM, but did not detect lateral specificity. Also, impairment in emotional encoding in BD is mediated by dysfunction in a circuit including the precuneus, medial frontal regions, and amygdala (Dickstein et al., 2007b; Rich et al., 2007; Glahn et al., 2010; Tseng et al., 2014), similar to the circuit in which we found aberrant resting connectivity.

We did not detect abnormal amygdala connectivity in SMD. This may be a type II error because, while amygdala iFC did not differ significantly in SMD vs. HV; the effect size was moderate (Cohen's d 's ≈ 0.4) for both clusters. Hulvershorn et al. (2013) also did not detect differences in amygdala iFC between HV and youths with ADHD plus high emotional lability, a phenotype resembling SMD (Merwood et al., 2014). However, Hulvershorn et al. (2013) found an association between parent rating of emotional lability in ADHD youth and iFC between the left amygdala and both bilateral frontal poles and the right medial PFC; notably, the direction of the finding was the opposite of what one would expect based on our findings. This inconsistency may be due to methodological differences, including how the irritable phenotype was operationalized. These findings support further study of the role that fronto-amygdala dysconnectivity may play in the pathophysiology of severe irritability in youth (Leibenluft and Stoddard, 2013).

Several limitations affect the interpretation of our study. An important limitation is that the left basolateral ROI is based on a probabilistic 2-mm isotropic atlas, resampled to the lower 3-mm isotropic, resolution of our functional images. Thus, our findings may have been influenced by neighboring structures, e.g., parahippocampal gyrus or anterior hippocampus. As a positive control, we verified that the connectivity map from the basolateral ROI in the HV group was similar to the basolateral amygdala iFC map in Roy et al. (2009), including the ipsilateral temporal pole, contralateral amygdala, and ventromedial PFC (Supplemental Image 2). Another limitation is that the patient groups had substantial psychiatric comorbidity. It is unlikely, however, that comorbid ADHD or anxiety disorders explain our results since these disorders were present in similar levels in BD and SMD. Furthermore,

post hoc analyses suggest that anxious and depressive symptoms at scanning did not explain the group differences in amygdala iFC. We did not collect validated dimensional measures of irritability or euphoria, but future research may examine their relationship to amygdala iFC. Similarly, while patients varied in their psychotropic medication regimens, *post hoc* analyses did not implicate a specific medication class in our findings. The BD group was restricted to a “narrow phenotype” of episodic mania to ensure broad consensus on BD diagnosis. This study provides no information on other phenotypes of BD, such as irritable only mania without grandiosity, or BD not otherwise specified. Images were acquired with three different scanners. Though multiple scanners have been successfully used in investigations of iFC in mental disorders (e.g., Roy et al. 2013) and scanner was added as a covariate, scanner-specific signal-to-noise ratios and geometric distortions may influence the results.

In sum, we found that amygdala iFC distinguished BD and SMD, suggesting a distinct neural basis for the two disorders. While SMD is a research diagnosis, it represents a clinical population defined by severe, chronic irritability which is of interest in child psychopathology (Leibenluft and Stoddard, 2013). Furthermore, all but one of our SMD participants would meet criteria for the novel DSM-5 diagnosis of DMDD, suggesting that our current results may advance what is known about this new DSM-5 disorder. Though fronto-limbic abnormalities are common in mental disorders, these findings suggest that the specific nature of these abnormalities may differ amongst disorders. These findings should guide further investigation of the neural basis of these clinically important phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Youths with a history of episodic hypomania or mania (BD) differ from youths with severe, chronic irritability (SMD) in intrinsic functional connectivity (iFC) between the left basolateral amygdala and the medial prefrontal cortex, posterior cingulate, and precuneus--suggesting that they are distinct clinical phenotypes.
- Relative to healthy volunteers, those with BD show increased iFC between the amygdala and these regions, suggesting hyperconnectivity between the amygdala and prefrontal cortex, precuneus, and posterior cingulate is a feature of BD.

Fig. 1. Non-overlapping amygdala regions of interest at $y=-6$ in MNI space, following Roy and colleagues (2009) displayed over the MNI $n=152$ averaged template. Red = centromedial, blue = basolateral, and green = superficial. Voxels assigned to each region from FSL's Juelich probability atlas at a 50% probability threshold.

Fig. 2. Left basolateral iFC to a posterior cluster differs between the BD, SMD, and HV groups, $p=0.00008$, cross-hairs at peak voxel, $k=65$. The boxplot displays *post hoc* differences in iFC (mean Fisher's z), with $BD>HV$, $BD>SMD$, and $HV=SMD$ (Holm-Bonferroni corrected t -tests; p 's = 0.002, <0.001, and 0.21, respectively).

Fig. 3.

Left basolateral iFC to a medial prefrontal cluster differs between the BD, SMD, and HV groups, $p=0.0003$, cross-hairs at peak voxel, $k=48$. The boxplot displays *post hoc* differences in iFC (mean Fisher's z), with $BD>HV$, $BD>SMD$, and $HV=SMD$ (Holm-Bonferroni corrected t -tests; p 's = 0.005, <0.001, and 0.21, respectively).

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 (SD)	14.3 (2.3)	13.9 (2.5)	14.6 (2.5)	$F(2,50)=0.36, p=0.70$
IQ ^c , mean (SD)	108.4 (10.4)	107.2 (12.1)	103.3 (12.7)	$F(2,44)=0.73, p=0.49$
YMRS ^c score, mean (SD)			8.5 (6.6)	
CDRS ^c score, mean (SD)		25.2 (4.2)	27.5 (9.4)	$t(15.4)=0.82, p=0.42$
PARS ^c score, mean (SD)		12.5 (5.7)	13.3 (5.2)	$t(25.2)=0.37, p=0.71$
CGAS ^c score, mean (SD)		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; YMRS= 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; SoPh=social phobia.

^b Eleven BD youths met criteria for BD I and 3 met for BD II.

^c IQ was missing for 6 participants (1 BD, 3HV, and 2 SMD). YMRS, PARS, CDRS, and medication data missing for one BD participant. CGAS data missing for another BD participant and an 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 ≤ 12 and CDRS ≥ 40 . For BD only, hypomanic limits were YMRS > 12 but < 26 and CDRS < 40 , mania limits were YMRS ≥ 26 and CDRS < 40 , and mixed state limits were YMRS > 12 and CDRS ≥ 40 .

^e All medication comparisons are between BD and SMD only.

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Table 2MRI characteristics^a

	HV n=20	SMD n=19	BD n=14	Comparison
Censored volume to volume motion, mm, mean (SD) ^b	0.062 (0.028)	0.073 (0.023)	0.068 (0.025)	$F(2,50)=0.88, p=0.42$
Global correlation, r , mean (SD)	0.064 (0.044)	0.077 (0.043)	0.066 (0.031)	$F(2,50)=0.54, p=0.59$
Scanner n (%)				
Scanner 1	12 (60)	5 (26)	4 (29)	
Scanner 2	2 (10)	5 (26)	7 (50)	
Scanner 3	6 (30)	9 (47)	3 (21)	

^aHV=healthy control; SMD=severe mood dysregulation; BD=bipolar disorder.^bEuclidean mean of the volume to volume shift in echoplanar images for all volumes entered into analysis.