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Cerebral Blood Flow and Mood in Adolescents With Bipolar Disorder

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Objective: Multiple prior studies have examined cerebral blood flow (CBF) in relation to mood states in adults with bipolar disorder (BD). This study examined CBF related to mood states in adolescents early in the course of BD, about which little is known.

Method: The study recruited 155 adolescents (mean [SD] age = 17.23 [1.62] years), including 81 with BD (32 hypomanic/mixed, 25 depressed, 24 euthymic) and 74 healthy controls. CBF was ascertained using pseudocontinuous arterial spin labeling magnetic resonance imaging. Region-of-interest analysis (amygdala, anterior cingulate cortex, middle frontal gyrus) controlling for age, sex, and race was complemented by whole-brain voxel-wise analyses. Within-BD regression analysis using age and sex as covariates examined the association of mania and depression severity with CBF.

Results: In region-of-interest analyses, there were no group differences in CBF. Within the overall BD group, higher depression scores were associated with lower anterior cingulate cortex CBF ($\beta = -.27$, $p = .01$). In corrected voxel-wise analyses, CBF in the euthymic BD group was significantly higher compared with healthy controls in temporal and precentral regions.

Conclusion: The finding of elevated regional CBF in adolescents with euthymic BD diverges from prior findings of reduced regional CBF in adults with BD. Higher CBF in adolescents with euthymic BD may reflect a developmentally specific compensatory perfusion mechanism required to maintain euthymia. However, longitudinal studies are needed to understand the temporal association of CBF and mood state in adolescents with BD, ideally followed into adulthood.

Plain language summary: Cerebral blood flow, which is the amount of blood that is delivered to the brain, may be impacted in bipolar disorder. This study compared a group of adolescents with bipolar disorder in different mood states with a control group of adolescents without bipolar disorder. This study found that lower cerebral flow in brain regions associated with mood regulation is inversely correlated with depressive symptoms, and that adolescents with bipolar disorder who are not currently in a mood episode had higher cerebral blood flow that may be developmentally adaptive.

Diversity & Inclusion Statement: We worked to ensure sex and gender balance in the recruitment of human participants. We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. We worked to ensure that the study questionnaires were prepared in an inclusive way. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented sexual and/or gender groups in science. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group. The author list of this paper includes contributors from the location and/or community where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

Key words: adolescents; bipolar; mood; neuroimaging

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Bipolar disorder (BD) is a severe chronic mood disorder characterized by manic and hypomanic episodes generally alternating with depressive episodes.[1] Onset of BD before adulthood is common, and in such cases symptomatic burden and overall disease severity are increased.[2] Indeed, the longitudinal course of BD in youth is characterized by 60% of time spent symptomatic with depressive symptoms predominating.[3] In addition to the impact on mental health and functioning, greater symptomatic burden of BD is associated with increased risk of cardiovascular risk factors, cardiovascular disease, and mortality.[4]

Classical functional neuroimaging in BD implicates frontolimbic-subcortical network dysfunction, with abnormal connectivity between the amygdala and regions involved in emotional processing, such as the anterior cingulate cortex (ACC), but more recent work has also implicated large-scale brain networks such as the default

mode network, the salience network, the cognitive control network, and the sensorimotor network.[5,6] Mood states appear to map onto regional differences in functional activation and connectivity among adults with BD.[7] The vast majority of these functional magnetic resonance imaging (MRI) studies are based on blood oxygenation level–dependent signal, which reflects not only neuronal processes but also cerebral blood flow (CBF).[8] CBF is quantified as the volume of blood delivered to brain tissue per minute and the basal physiological rate scales with metabolic demand (ie with oxygen and glucose as substrates).[9] In a recent review of 33 case-control studies comprising 508 adults with BD and 538 controls, reported decreased CBF in frontal and temporal regions in adults with BD during depression compared with controls was prevalent, although exceptions exist.[10]

Our group has conducted 3 studies of CBF in adolescents with BD. In a preliminary study, our group found increased CBF in medial frontal and middle cingulate regions in 31 adolescents with BD compared with 20 healthy control (HC) adolescents; although there were no significant associations between CBF and mood symptoms, that preliminary study was not powered to evaluate such associations.[11] Another study examined cerebral metabolic rate of oxygen consumption and found higher CBF in adolescents with BD compared with HCs, but it did not examine mood severity.[12] Most recently, we examined the association between CBF and individual core mood symptoms, finding that depressed mood severity was negatively associated with ACC and global CBF.[13] In the current study, we expanded on the findings in the previous studies aiming to determine whether CBF varies across different mood states in adolescents with BD.

We sought to build on prior findings in the current study by conducting both a categorical analysis examining mood states (ie, currently hypomanic/mixed, depressed, or euthymic) and a dimensional analysis (ie, overall manic and depressive symptom severity) in relation to CBF. We examined CBF across 4 groups (adolescents with BD currently hypomanic/mixed, depressed, or euthymic and HCs) in a priori regions of interest (ROIs) based on a review of previous literature on CBF in BD and on the neurofunctional model of BD[10]: ACC, middle frontal gyrus, and amygdala. Given the overall limited literature on CBF in BD, we completed the ROI analysis with whole-brain vertex-wise analysis, with the hope of informing future studies.

We hypothesized that there would be significant differences in CBF across groups, such that CBF would be lower in the BD depressed group as compared with the control group. Furthermore, we posited that overall depressive symptom severity would be inversely correlated with CBF.

METHOD

English-speaking participants aged 13 to 20 years were recruited from a subspecialty clinic and research program in an academic health sciences center. In addition, HCs were recruited from the community through advertisements. A total of 156 participants were enrolled; 1 participant was removed due to head motion artifact and insufficient image quality. This yielded a final sample of 155 participants, including 32 in the BD hypomanic/mixed group, 25 in the BD depressed group, 24 in the BD euthymic group, and 74 in the HC group.

Participants with BD were included if they met criteria for bipolar I disorder, bipolar II disorder, or BD not otherwise specified. BD not otherwise specified was defined using criteria previously operationalized by the COBY (Course and Outcome of Bipolar Illness in Youth) study group.[14] HC participants had no lifetime mood or psychotic disorders, alcohol or drug dependence disorders, or anxiety disorders within the past 3 months and no first- or second-degree family history of BD or psychotic disorders. Participants were excluded in the case of contraindication to MRI; cardiac, autoimmune, or inflammatory illness; neurological or cognitive impairment; or inability to provide consent.

Psychiatric diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School Age Children–Present and Life Version (K-SADS-PL)[15] with expanded mood sections, the 13-item K-SADS mania rating scale (MRS) (score range 0-65) and the 13-item K-SADS depression rating scale (DRS) (score range 0-67), in place of the standard mood sections of the K-SADS-PL.[16] Participants and their parent or guardian were interviewed, and a consensus score was established. Current mood was defined and operationalized as the worst week in the past month. Hypomania was defined as MRS score $\geq$12,[17] and depression was defined as DRS score $\geq$13.[18] These definitions were derived from previous literature[17] and from previous work from our group.[18] Youth with BD were divided into 3 subgroups: hypomanic/mixed (MRS score $\geq$12 and DRS score $\geq$13), depressed (DRS score $\geq$13 and MRS score $<$12), and euthymic (DRS score $<$13 and MRS score $<$12). Family psychiatric history was evaluated using the Family History Screen interview.[19] Functional impairment was evaluated using the Children's Global Assessment Scale (CGAS).[20]

All participants as well as one parent or guardian provided written informed consent before study participation. The study was approved by the local research ethics board.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TABLE 1 Demographic and Clinical Variables

	HC group (n = 74)		BD hypomanic/ mixed group (n = 32)		BD depressed group (n = 25)		BD euthymic group (n = 24)		Statistics	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	***F* or χ^2**	***p***
Age, y	17.03	(1.8)	16.83	(1.5)	18	(1.36)	17.54	(1.22)	$F = 3.3$	.02
	n	(%)	n	(%)	n	(%)	n	(%)		
Race, White	42	(56.8)	26	(81.3)	19	(76)	16	(66.7)	$\chi^2 = 7.23$	.06
Sex, Female	38	(51.4)	25	(78.1)	12	(48)	14	(58.3)	$\chi^2 = 7.64$	.05
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
SES	4.36	(0.92)	4.03	(0.97)	4.64	(0.7)	4.17	(0.92)	$F = 2.44$	.07
Age at onset, y	—		14.43	(2.42)	15.8	(1.7)	14.28	(3.43)	$F = 2.69$	.07
BD subtype										
	n	(%)	n	(%)	n	(%)	n	(%)		
BD-I	—		8	(25)	9	(36)	13	(54.2)	$\chi^2 = 5.31$	.26
BD-II	—		10	(31.3)	8	(32)	5	(20.8)		
BD-NOS	—		14	(43.8)	8	(32)	6	(25)		
Lifetime comorbidity										
Substance use disorder	—		9	(28.1)	6	(24)	4	(16.7)	$\chi^2 = 1.01$	.60
ADHD	—		18	(56.3)	11	(44)	8	(33.3)	$\chi^2 = 2.94$	.23
Anxiety disorder	—		29	(90.6)	19	(76)	15	(62.5)	$\chi^2 = 6.34$	.04
Family history of BD	—		18	(56.3)	11	(44)	10	(41.7)	$\chi^2 = 1.42$	.49
Lifetime medication										
SGA	—		24	(75)	19	(76)	17	(70.8)	$\chi^2 = 0.19$	.91
Lithium	—		6	(18.8)	6	(24)	8	(33.3)	$\chi^2 = 1.58$	.45
Antidepressant (SSRI)	—		11	(34.4)	10	(40)	4	(16.7)	$\chi^2 = 3.43$	.18
Stimulant	—		7	(21.9)	2	(8)	8	(33.3)	$\chi^2 = 4.74$	.09
Current medication										
SGA	—		21	(65.6)	14	(56)	13	(54.2)	$\chi^2 = 0.91$	.64
Lithium	—		3	(9.4)	6	(24)	6	(25)	$\chi^2 = 2.94$	.23
Antidepressant (SSRI)	—		5	(15.6)	3	(12)	0	(0)	$\chi^2 = 3.47$	.18
Stimulant	—		3	(9.4)	1	(4)	1	(4.2)	$\chi^2 = 0.94$	.63
Clinical scores										
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
Mania score—current	0.26	(0.92)[b]	20.63	(6.53)[a,c,d]	1.88	(2.44)[b]	2.08	(3.73)[b]	$F = 270.31$	<.001
Mania score—lifetime most severe	0.72	(1.75)[b,c,d]	31.44	(10.16)[a]	30.36	(10.48)[a]	31.21	(11.56)[a]	$F = 196.04$	<.001
Depression score—current	0.66	(1.71)[b,c]	19.91	(9.76)[a,c,d]	24.20	(7.42)[a,b,d]	3.67	(4.43)[b,c]	$F = 157.1$	<.001

(*continued*)

TABLE 1 Continued

	HC group (n = 74)		BD hypomanic/mixed group (n = 32)		BD depressed group (n = 25)		BD euthymic group (n = 24)		Statistics	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*F* or χ^2	*p*
Depression score—lifetime most severe	1.99	(3.53)[b,c,d]	33.16	(10.4)[a,d]	32.52	(11.23)[a,d]	23.29	(11.87)[a,b,c]	$F = 153$	<.001
CGAS—current	88.91	(5.92)[b,c,d]	60.77	(8.39)[a,d]	61.6	(14.17)[a,d]	71.63	(11.8)[a,b,c]	$F = 99.08$	<.001
CGAS—highest past	89.08	(6.37)[b,c,d]	63.29	(9)[a,d]	68.68	(11)[a,d]	75	(9.96)[a,b,c]	$F = 85.87$	<.001
CGAS—most severe	79	(7.94)[b,c,d]	43.16	(8.73)[a]	42.76	(8.07)[a]	45.29	(9.59)[a]	$F = 15.98$	<.001

Note: Superscript letters designate pairwise post hoc contrasts with $p < .05$: a = HC; b = BD hypomanic/mixed; c = BD depressed; d = BD euthymic. ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BD-NOS = bipolar disorder not otherwise specified; CGAS = Children's Global Assessment Scale; HC = healthy control; SES = socioeconomic status; SGA = second-generation antipsychotic; SSRI = selective serotonin reuptake inhibitor.

MRI Acquisition

MRI was performed with a 3T Philips Achieva system (Philips Medical Systems, Best, the Netherlands) using a radiofrequency body coil transmission and an 8-channel head receiver coil for signal detection. The MRI protocol included acquisition of T1-weighted images for anatomical registration and CBF measurements using pseudocontinuous arterial spin labeling (ASL). Anatomical T1-weighted images were acquired using high-resolution fast field echo imaging (repetition time/echo time/inversion time = 9.5/2.3/1,400 ms, field of view 240 mm × 191 mm, spatial resolution 0.94 × 1.17 × 1.2 mm, flip angle 8°, 256 × 164 × 140 matrix, scan duration 536 seconds). For ASL, first, for planning, phase contrast angiography scout images were acquired to help visualize arterial and venous anatomy at the ASL labeling plane. The ASL images were then obtained with single-shot two-dimensional echo planar imaging (repetition time/echo time = 4,000/9.7 ms, 64 × 64 × 18 matrix, spatial resolution 3 × 3 × 5 mm), 1,650 ms labeling duration, postlabel delay of 1,600 ms for the most inferior slice, 30 control-tag pairs, and scan duration of 248 seconds. ASL reference images were acquired with a repetition time of 10 seconds to determine the initial magnetization used for quantification.[21]

ASL Processing

Processing of ASL data used the FMRIB Software Library (FSL), incorporating tools developed in the laboratory.[11,22] First, ASL data were coregistered to a reference volume. Next, difference images were produced from pairs of control (unlabeled) and tag (blood-labeled) images to provide a measure of CBF. Spatial smoothing of difference images was done using a 5-mm Gaussian kernel. A postprocessing procedure developed in the laboratory was used for head motion.[23] This method automatically determines the optimal number of intermediate perfusion images without using a head motion threshold. The mean of the remaining images after motion correction was used to measure CBF signal.[23] CBF estimates were converted to absolute units (mL/100 g/min).[21] For ROI analysis, T1-weighted images were coregistered to the Montreal Neurological Institute whole brain template, MNI152, standard brain, and masks were then transformed to individual ASL space for ROI CBF extraction.

Anatomical Image Processing

T1-weighted images were processed using FSL tools as follows: brain extractions were performed using BET for removing nonbrain tissue and skull stripping.[24] Images were coregistered to ASL space and standard space (the latter was done using MNI152), with FLIRT linear registration.[25]

TABLE 2 Regional Cerebral Blood Flow in Adolescents With Bipolar Disorder (BD) Across Mood States and in Healthy Control (HC) Adolescents

	HC group (n = 74)		BD hypomanic/mixed group (n = 32)		BD depressed group (n = 25)		BD euthymic group (n = 24)		Statistics		
ROI	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*F*	Partial η^2	*p*
Global GM	63.41	(11.38)	67.48	(11.97)	59.71	(11.91)	68.52	(12.09)	2.16	0.04	.1
ACC	72.69	(15.43)	77.60	(14.21)	68.42	(14.77)	78.88	(15.40)	2.05	0.04	.11
MFG	82.09	(16.08)	87.97	(18.77)	75.73	(15.68)	87.11	(16.57)	1.67	0.03	.18
Amygdala	39.96	(11.06)	44.06	(9.20)	40.62	(10.74)	44.83	(11.49)	1.31	0.03	.27

Note: *Cerebral blood flow is reported in mL/100 g/min. ACC = anterior cingulate cortex; GM = gray matter; MFG = middle frontal gyrus; ROI = region of interest.*

Intensity normalization and segmentation of subcortical gray and white matter from extracted brains were obtained using FAST.[26]

Defining ROIs

ROIs were selected based on regions previously found in BD CBF studies.[10] The ROIs included ACC (anterior division of cingulate gyrus), middle frontal gyrus (structural definition of the functional region dorsolateral prefrontal cortex), and amygdala. In addition to these ROIs, we also investigated global gray matter CBF, extracted from gray matter voxels obtained from segmentation. ROIs were defined using parcellation from Harvard-Oxford Cortical and Subcortical Structural Atlases in FSL in 2-mm standard space.[27] Commands within FSL were used to create the ROIs.[22] Bilateral ROI masks were split between left and right hemispheres.

Statistical Analysis

ROI analyses were performed using IBM SPSS version 24 (IBM Corp., Armonk, NY). Group comparisons of participant demographics and clinical variables were assessed using one-way analysis of variance and χ^2 tests, as appropriate. Analysis of covariance models evaluated between-group differences in ROI CBF, including age, sex, and race as covariates. Omnibus tests comparing ROI CBF across the groups were followed by post hoc pairwise comparisons when significant. The false discovery rate correction method was used to correct for multiple comparisons. A within-BD regression analysis of ROIs and MRS and DRS scores included age and sex mean-centered covariates. Similarly, false discovery rate correction was used.

Regarding whole-brain analyses, a general linear model was used with age, sex, and race as covariates, employing the FSL tool FLAME1.[28] Post hoc pairwise tests were then conducted to determine which groups were significantly different from one another. The effect size of post hoc pairwise differences were reported using Cohen *d*. CBF–mood associations were also analyzed within the BD group using a general linear model with mood scores (ie, DRS, MRS) as the predictor and age, sex, and race as covariates. In both of these analyses, cluster-based thresholding was used with a voxel threshold *z* value of 1.96 for a significance level of $p = .05$. Finally, FSL cluster command was used to apply cluster correction, and cluster extent–based threshold was calculated using Gaussian random field theory; significant clusters were defined as $p < .05$.

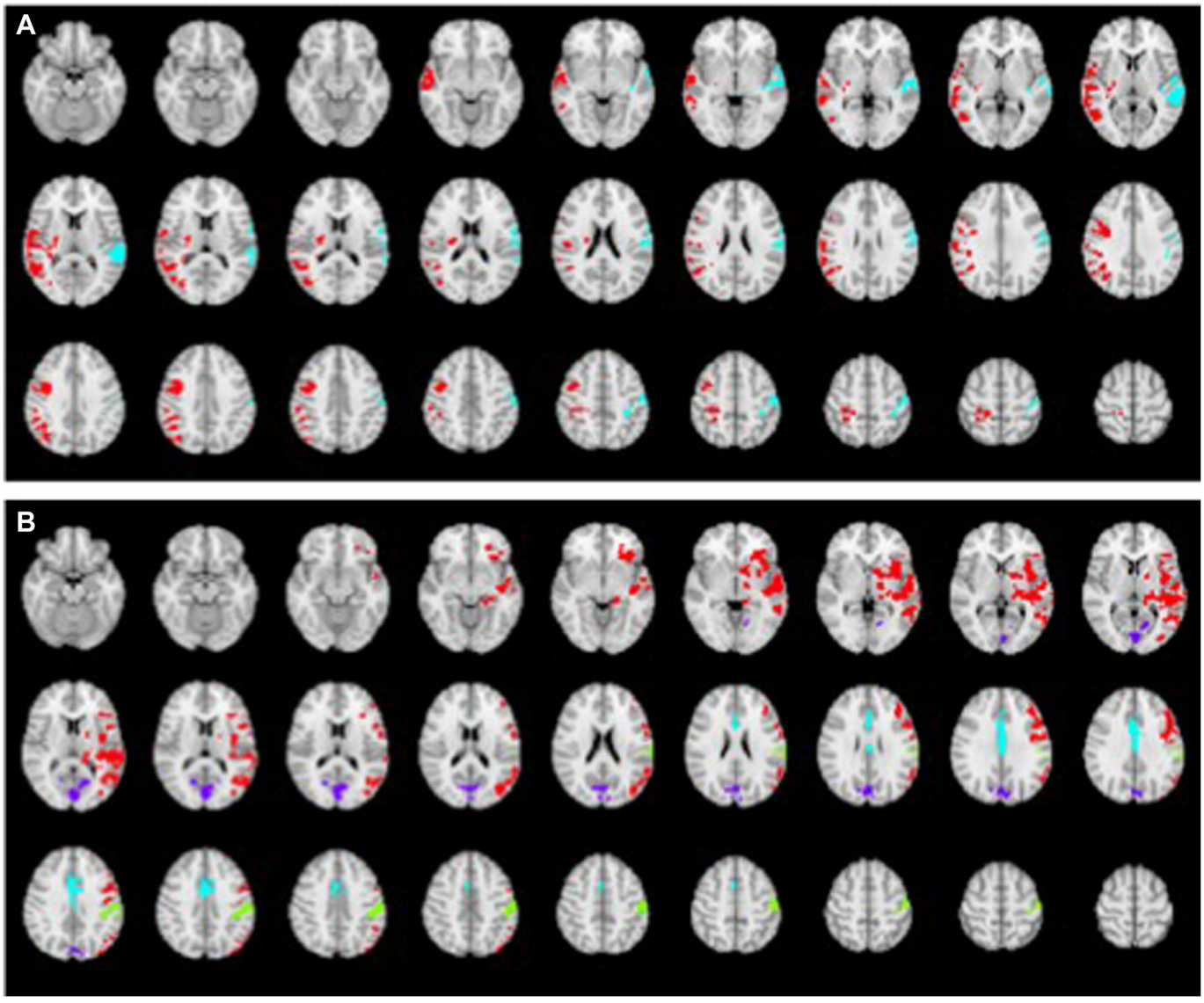
Exploratory sensitivity analyses were also done for the ROI analyses as follows: removing participants with hypomania from the combined hypomania/mixed group and adjusting for BD subtype and for common medications (current second-generation antipsychotic use, current lithium use, and current selective serotonin reuptake inhibitor use).

RESULTS

Demographic and Clinical Characteristics

Table 1 presents demographic and clinical variables for 155 adolescents, including 81 with BD (32 hypomanic/mixed, 25 depressed, 24 euthymic), and 74 HCs. Within the hypomanic/mixed group, 22 adolescents were defined as having mixed hypomania, and 6 were defined as having pure hypomania. In 4-way analyses, there were significant between-group differences in age ($p = .02$) and sex ($p = .05$). Race was nearly significantly different ($p = 0.06$) and was therefore also included as a covariate. There were no differences in terms of socioeconomic status when comparing the 4 groups ($p = .07$). There were significant differences between the 3 BD groups in terms of age ($F = 5.26$, $p = .007$) and socioeconomic status ($F = 3.57$, $p = .03$), but not in terms of other demographic characteristics or clinical characteristics. Current depression scores were higher in the depressed group than in the hypomanic/mixed group ($p = .03$).

FIGURE 1 Group Differences in Cerebral Blood Flow in Whole-Brain Analyses



Note: (A) Clusters associated with significant between-group differences. Red represents cluster with peak at right precentral gyrus, and blue represents cluster with peak at left planum temporale (Table 1). (B) Depressive symptom severity associations with cerebral blood flow in voxel-wise analysis. Red represents cluster with peak at left superior temporal gyrus, purple represents cluster with peak at calcarine cortex, blue represents cluster with peak at cingulate gyrus, and green represents cluster with peak at left postcentral gyrus (Table 1).

Mean CGAS scores were significantly higher in the HC group than in the BD groups ($p < .001$) and significantly higher in the BD euthymic group than in the BD hypomania/mixed group ($p < .001$) and the BD depressed group ($p = .001$) (Table 1).

ROI CBF Analysis

CBF values for the selected ROIs (amygdala, middle frontal gyrus, and ACC) and for total GM CBF are presented by group in Table 2. There were no significant between-group differences for any of the ROIs.

Within-BD regression analyses demonstrated a negative association between DRS score and ACC CBF ($\beta = -.27$, $p = .01$). This remained significant after false discovery rate correction ($p = .05$). There were no other significant findings relating to dimensional mood symptoms in ROI analyses.

Whole-Brain CBF Analysis

A whole-brain voxelwise analysis revealed significant between-group differences in 2 clusters encompassing the right precentral, superior, and middle temporal gyri as well

TABLE 3 Vertex-Wise Analysis Clusters From Between-Group Differences in Cerebral Blood Flow (CBF) and Association of Depression Scores With CBF in the Bipolar Disorder (BD) Group

Peak cluster region	Additional regions	Size of cluster (voxels)	*p*	MNI X	MNI Y	MNI Z	β
Between-group differences in CBF							
Right precentral gyrus	Right superior temporal gyrus, right middle temporal gyrus	1,060	<.001	39	−6	36	NA
Left planum temporale	Left superior temporal gyrus	441	<.001	−60	−30	9	NA
Association of depression scores with CBF in youth with BD							
Left superior temporal gyrus	Planum temporale, planum polare, left middle temporal gyrus, insular cortex, precentral gyrus	1,494	<.001	−54	−18	−3	−.38
Calcarine cortex	Lingual gyrus, occipital pole, cuneal cortex	298	.007	−3	−84	6	−.36
Cingulate gyrus	NA	284	.009	0	3	30	−.32
Left postcentral gyrus	Left anterior supramarginal gyrus	224	.03	−60	−21	45	−.38

Note: *MNI = Montreal Neurological Institute; NA = not applicable.*

as the left planum temporale and superior temporal gyrus (Figure 1A; Table 3). Post hoc analyses of the right precentral gyrus (Figure 2) revealed that the BD euthymic group had higher CBF than the HC ($p < .001$, $d = 0.89$), BD depressed ($p < .001$, $d = 1.17$), and BD mixed/hypomanic ($p < .05$, $d = 0.62$) groups. Additionally, the BD mixed/hypomanic group had higher CBF than the BD depressed group ($p < .05$, $d = 0.54$) in the right precentral gyrus. Post hoc analyses of the left planum temporale (Figure 2) revealed that the BD euthymic group had higher CBF than the HC ($p < .001$, $d = 1.02$) and BD depressed ($p < .001$, $d = 1.56$) groups; additionally, the BD mixed/hypomanic group had higher CBF than the HC ($p = .007$, $d = 0.59$) and BD depressed ($p = .007$, $d = 0.73$) groups.

In the BD group, higher depressive symptom severity was associated with lower CBF in 4 clusters with peak regions within the left superior temporal gyrus, calcarine cortex, cingulate gyrus, and left postcentral gyrus, respectively (Figures 1B and 3; Table 3). There were no correlations between CBF and overall mania symptom severity.

Sensitivity Analyses

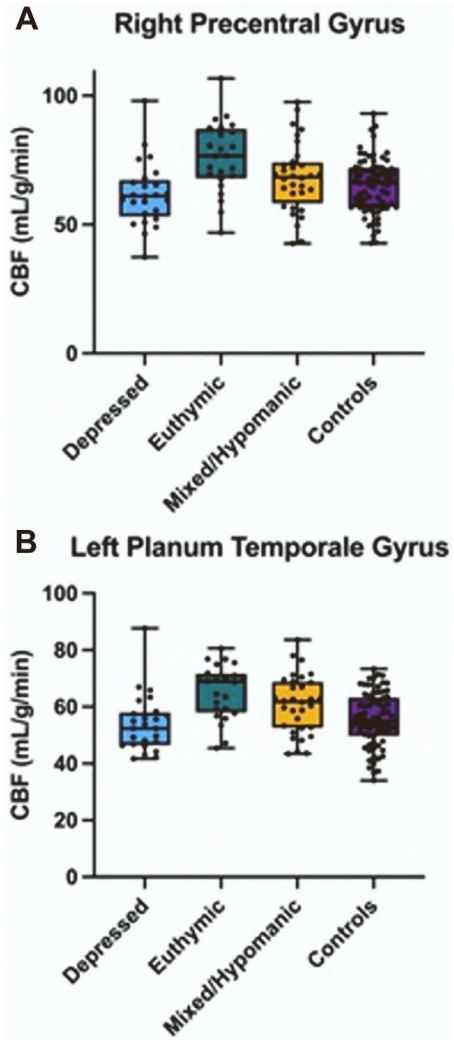
After removing the participants with pure hypomania from the combined BD hypomanic/mixed group (n = 6), there were no group differences in any of the ROIs. Similar to the results including the overall BD group, a negative correlation between depression scores and CBF in the ACC was found ($\beta = -.23$, $p = .04$). Upon adjustment for BD subtype, similarly to our main results, a negative correlation was found between depression scores and ACC CBF ($\beta = -.28$, $p = .01$). Similarly, adjusting for current second-generation antipsychotic use, current lithium use, and current selective serotonin reuptake inhibitor use, all results remained identical to main analyses.

DISCUSSION

This cross-sectional study investigated the association of CBF with mood, using categorical (ie, mood states) and dimensional (ie, overall depression and overall mania symptom severity) approaches in adolescents with BD. In ROI analyses, we did not find differences between CBF among the 4 groups, we found that higher depression was associated with lower ACC CBF within the overall BD group. In voxel-wise analyses, higher CBF was present in the BD euthymic group than in HC and symptomatic BD groups in temporal and precentral regions. Similar to the ROI findings, lower CBF was associated with greater depression severity within BD in regions encompassing the left superior temporal gyrus, cingulate cortex, calcarine cortex, and left post central gyrus. While our hypotheses anticipated abnormally reduced CBF in relation to depression, findings ultimately reflect elevated CBF during euthymia.

Our results differ from findings in symptomatic adults with BD, which demonstrated reduced CBF in frontal and temporal regions vs controls.[10] Present findings may relate in part to divergence from typical developmental trajectories in CBF, as CBF is known to decline in late adolescence in population samples.[29] Developmental differences in CBF are complex and demonstrate both regional variability and sex differences.[29] Gray matter pruning occurs in normal adolescence and is thought to follow a characteristic inverted U–shaped curve, with distinctive peak periods in various

FIGURE 2 Mean Cerebral Blood Flow (CBF) by Group in Whole-Brain Analyses



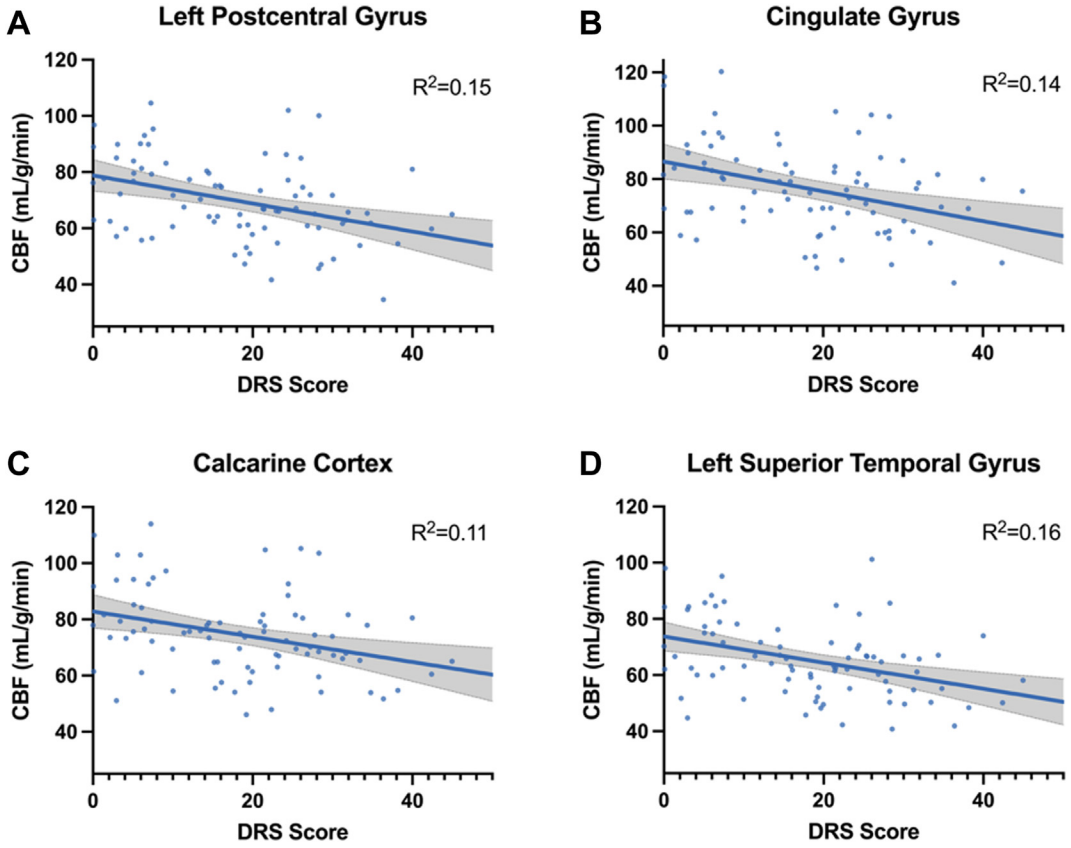
brain regions.[30] Studies have found abnormal developmental trajectories of gray and white matter volume among adolescents with BD, with putative delay in maturation.[31] In contrast, the developmental trajectory of CBF in adolescents with BD is unknown, and our study highlights the need for further longitudinal, repeated-measures research in this area.

Few studies have examined CBF in adolescents with mood disorders. A prior study in the same sample examining CBF in relation to individual mood symptoms found an overall similar pattern of results, with depressed mood having an inverse relationship with ACC and global gray matter CBF.[13] Our findings contrast those of a study comparing 25 adolescents with major depressive disorder with 26 controls, which found reduced CBF in the ACC, cerebellum, amygdala, insula, and inferior frontal and temporal regions and increased CBF in the subcallosal cingulate, putamen, and fusiform gyrus.[32] Another study of 21 adolescents with major depressive disorder found that CBF increased in the right dorsolateral prefrontal cortex, right caudate nucleus, and left inferior parietal lobe after 5 sessions of cognitive-behavioral therapy.[33] The present findings are consistent, however, with elevated CBF in the ACC, postcentral gyrus, medial temporal lobe, and midbrain, as was observed in youth with a lifetime history of mood disorders, anxiety disorders, and/or psychosis.[34] The current symptomatic status in those youth was unreported, limiting comparison with our study.[34]

Taken together, increased CBF in the BD euthymic group vs symptomatic BD groups and decreased CBF in relation to increasing depression symptoms could reflect a compensatory response to maintain euthymia in BD. There is normally a coupling between CBF and neural activation, which signifies that increased CBF is generally associated with increased local neuronal activity.[9] Importantly, the hemodynamic response, or changes in CBF with brain activation, also depends on energy metabolism and mitochondrial function.[35] Contemporary theories regarding the etiopathology of BD highlight abnormal energy metabolism and mitochondrial dysfunction.[36] Ineffective metabolic pathways in the context of impaired phosphorylation may lead to higher needs for glucose and oxygen, and in turn CBF, to maintain function.[37] Mitochondrial dysfunction also results in imbalance of reactive oxygen species, which may further damage vascular coupling via inhibition of vasodilation by interacting with nitric oxide and via direct endothelial damage.[38] These factors may underlie in part the association between depression symptoms and regional CBF.

The regions where significant findings were observed in the present study are relevant to BD and were found to have lower cortical thickness in participants with BD vs controls in a large international study of brain structure.[39] The ACC integrates emotional processes and is a brain region identified using structural and functional neuroimaging readouts in BD and major depressive disorder in contrast to controls, even during euthymia.[40,41] A study in adolescents with BD depression found that remission from depression was correlated with increased ACC activation during an emotion processing task at baseline.[42] A meta-analysis of BD functional correlates found ACC hypoactivation in BD, more so in youth with BD youth than in adults with BD, which may speak to the importance of developmental considerations.[43] Similarly, temporal and precentral regions are thought to be implicated in

FIGURE 3 Association of Depression Symptom Severity With Cerebral Blood Flow in Whole-Brain Analyses



Note: *(A) Left postcentral gyrus. (B) Cingulate gyrus. (C) Calcarine cortex. (D) Left superior temporal gyrus. CBF=cerebral blood flow; DRS=depression rating scale.*

multimodal integration of complex auditory and visual emotional information.[44] Functional MRI studies in pediatric BD report on abnormal connectivity of the superior temporal cortex.[45] One study reported hyperactivation of superior temporal regions specifically during emotion processing in euthymic youth with BD.[46]

Several limitations must be considered when interpreting our findings. First, our cross-sectional design did not allow us to evaluate for within-person changes in CBF in relation to mood states and chronological age. Second, despite being the largest study to date on this topic, the sample was not large enough to evaluate hypomanic and mixed groups separately. Similarly, there was limited variability in manic symptoms, which reduced power to detect associations with CBF. Finally, as with most BD studies, our sample was characterized by significant heterogeneity in BD subtype, comorbidity, and medication. We chose to include youth with all BD subtypes to be representative of this population, but acknowledge this as an important limitation. Larger studies are warranted that are powered for more comprehensive covariate modeling (eg, BD subtype, psychiatric comorbidities, treatments) when evaluating neuroimaging correlates of mood states.

In conclusion, we found that mood states and overall depression severity were associated with CBF in adolescents with BD. In particular, our results suggest that CBF in adolescents with BD may differ from CBF in HCs most prominently during euthymia, rather than hypomanic/mixed or depressed states. We speculate that this finding may reflect a compensatory mechanism, perhaps required to mitigate anomalous energy metabolism and oxidative stress. Future studies are warranted to evaluate the temporal association of CBF with mood states and mood symptoms in adolescents with BD. Future studies should also integrate cognitive function, given recent findings linking CBF with cognition in BD,[47] oxidative stress markers in regard to

mood states in BD,[48] and markers of energy metabolism such as ^{31}P-MRS to further examine the hypothesis regarding compensatory mechanisms. Finally, studies of CBF in unaffected adolescents at familial/genetic risk for BD are warranted to identify putative markers of vulnerability and/or resilience. Contrasting numerous structural, functional, and diffusion tensor imaging studies in adolescent BD, there is clearly a paucity of data regarding CBF. Expanding the knowledge base regarding CBF in adolescent BD has the potential to yield unique and thus far unrealized insights to complement and extend the findings from these other neuroimaging phenotypes.

CRediT authorship contribution statement

Simina Toma: Writing – original draft, Methodology, Investigation, Conceptualization. **Mikaela K. Dimick:** Writing – review & editing, Data curation. **Anahit Grigorian:** Writing – review & editing, Formal analysis, Data curation. **Lisa Fiksenbaum:** Validation, Methodology, Formal analysis. **Andrew D. Robertson:** Writing – review & editing, Methodology, Formal analysis. **Kody G. Kennedy:** Writing – review & editing, Validation, Formal analysis, Data curation. **Rachel H.B. Mitchell:** Writing – review & editing, Methodology. **Bradley J. MacIntosh:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Benjamin I. Goldstein:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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