

REGULAR RESEARCH ARTICLE

Obesity and Cerebral Blood Flow in the Reward Circuitry of Youth With Bipolar Disorder

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Abstract

Background: Bipolar disorder (BD) is associated with elevated body mass index (BMI) and increased rates of obesity. Obesity among individuals with BD is associated with more severe course of illness. Motivated by previous research on BD and BMI in youth as well as brain findings in the reward circuit, the current study investigates differences in cerebral blood flow (CBF) in youth BD with and without comorbid overweight/obesity (OW/OB).

Methods: Participants consisted of youth, ages 13–20 years, including BD with OW/OB (BD_{OW/OB}; n=25), BD with normal weight (BD_{NW}; n=55), and normal-weight healthy controls (HC; n=61). High-resolution T1-weighted and pseudo-continuous arterial spin labeling images were acquired using 3 Tesla magnetic resonance imaging. CBF differences were assessed using both region of interest and whole-brain voxel-wise approaches.

Results: Voxel-wise analysis revealed significantly higher CBF in reward-associated regions in the BD_{NW} group relative to the HC and BD_{OW/OB} groups. CBF did not differ between the HC and BD_{OW/OB} groups. There were no significant region of interest findings.

Conclusions: The current study identified distinct CBF levels relating to BMI in BD in the reward circuit, which may relate to underlying differences in cerebral metabolism, compensatory effects, and/or BD severity. Future neuroimaging studies are warranted to examine for changes in the CBF-OW/OB link over time and in relation to treatment.

Keywords: Bipolar disorder, youth, body mass index, cerebral blood flow, reward circuit

Introduction

In adults with bipolar disorder (BD), there are high rates of obesity in both epidemiologic and clinical samples, and comorbid obesity is associated with a more severe course

of illness, including increased risk of hospitalization and suicidality (Fagiolini et al., 2004; McIntyre et al., 2007; Goldstein et al., 2011, 2013; McElroy and Keck, 2012). In youth BD, there

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Significance Statement

This study examines the association between brain perfusion and obesity early in the course of bipolar disorder (BD), with fewer years of exposure to symptoms, medical comorbidities, and medications. In BD, obesity is common and correlates with more severe illness. The following groups were thus examined: BD with comorbid overweight/obesity (OW/OB), BD with normal weight (NW), and NW healthy controls (HC). Voxel-wise analyses revealed higher regional cerebral blood flow (CBF) among BD_{NW} in reward-associated regions compared with HC and BD_{OW/OB} groups. The current findings contribute to the sparse literature examining the relationship between CBF and obesity or body mass index (BMI) among individuals with BD. The BD subgroup differences may reflect differences in cerebral metabolism, compensatory failure to meet increased perfusion demands in BD_{OW/OB} and/or symptom severity. Future longitudinal studies using neuroimaging, through establishing imaging biomarkers, could enhance our understanding of the CBF-OW/OB association, thereby improving diagnostic and treatment modalities.

is increased prevalence of overweight/obesity (OW/OB) in clinical, but not epidemiologic, samples (Goldstein et al., 2008, 2016; Shapiro et al., 2017). Similar to adults, OW/OB is associated with more severe illness among youth with BD in both epidemiologic and clinical samples (Goldstein et al., 2008, 2016; Shapiro et al., 2017). Neurocognitive and neuroimaging correlates of emotional processing and reward dysfunction are reported in BD and obesity independently, suggesting a possible common pathophysiology (Rosen and Rich, 2010; Lopresti and Drummond, 2013; Arjmand et al., 2018). Relatedly, a prior study found that increased waist circumference is linked to increased reward-related impulsivity among youth with BD (Naiberg et al., 2016).

Non-psychiatric studies in adults show that BMI is associated with lower gray matter (GM) volume in the prefrontal cortex (PFC), hippocampus (Kurth et al., 2013), thalamus, and anterior cingulate cortex (ACC) (Wang et al., 2017). Youth neuroanatomical studies are largely consistent with adult literature, wherein increased BMI is associated with decreased GM volume of hippocampus (Bauer et al., 2015), amygdala (Alosco et al., 2014), and PFC (Laurent et al., 2020). There are, however, exceptions in literature, such as a correlation between BMI and increased GM volume (Saute et al., 2018) and a null finding in youth (Sharkey et al., 2015). Resting state functional connectivity studies have predominantly linked higher BMI to disrupted connectivity between key regions of the salience network (e.g., nucleus accumbens [NAc], amygdala, dorsal striatum) and the default mode network (e.g., PFC, inferior parietal lobe) (Black et al., 2014; Chodkowski et al., 2016; Hogenkamp et al., 2016; Contreras-Rodríguez et al., 2017; Meng et al., 2018; Zhang et al., 2019). Accordingly, there is evidence of obesity-related differences in brain metabolism. Cerebral blood flow (CBF) is a measure of rate of blood volume supplied per unit mass of tissue, with units of mL/100 g/min by convention (Fantini et al., 2016). Through neurovascular coupling, CBF supplies metabolically active regions with glucose and oxygen (Toma et al., 2018). In addition to supporting energy demands and regulating homeostasis, CBF has been linked to vascular risk factors (Jennings et al., 2013), making it an important metric of brain health. Despite this heuristic link between BMI and CBF, there is a paucity of research on this subject. Two studies report that higher BMI in adults is associated with lower CBF and lower glucose utilization in the PFC (Volkow et al., 2010; Willeumier et al., 2011).

Structural and functional neuroimaging studies in BD yield overlapping findings with those of obesity (Frazier et al., 2005; Pfeifer et al., 2008; Selvaraj et al., 2012; Satterthwaite et al., 2015; Altinay et al., 2016; Roberts et al., 2017; Sharma et al., 2017; Wei et al., 2017; Shi et al., 2018). Few neuroimaging studies have examined BMI in the context of BD. Higher BMI among adults with BD has been associated with reduced GM and white matter (WM) volumes in frontal, temporal, and limbic regions (Bond et al., 2011, 2014) and with reduced WM integrity in cortico-limbic

circuits (Mazza et al., 2017). Higher BMI among youth with BD has been associated with reduced cortical thickness in the PFC, medial orbitofrontal cortex (OFC), and caudal ACC to a greater extent than in HC (Islam et al., 2018). In adults with BD, although there is evidence of increased CBF in regions including the posterior cingulate cortex, middle temporal gyrus, precentral gyrus, precuneus, caudate, and putamen, the most consistent findings are of lower CBF during depressive and manic episodes in the left frontal, temporal, and parietal regions (Toma et al., 2018). In youth with BD, our group previously reported elevated global CBF (Karthikeyan et al., 2019) as well as higher CBF in medial frontal and middle cingulate regions (MacIntosh et al., 2017). Thus far, there are no studies examining CBF in relation to obesity or BMI among youth with BD. Normative changes in CBF levels coincide with changes in metabolic substrate levels (i.e., glucose and oxygen) throughout the lifespan (Chugani et al., 1987) and are reflective of developmental events such as neuronal growth and subsequent pruning (Giedd et al., 1999). Adolescence is therefore a critical period during which any illness-related divergence in CBF levels may be especially important.

Given that OW/OB and CBF are each indicators of metabolism and vascular risk (Jennings et al., 2013; Toma et al., 2018), we set out to examine the association between OW/OB and CBF in youth BD. We used arterial spin labeling (ASL) to investigate the relationship between CBF and BMI. Unlike nuclear medicine methods that use exogenous radioactive tracers, ASL is a noninvasive magnetic resonance imaging (MRI) technique that uses blood water as an endogenous tracer (Toma et al., 2018). Based on previous abnormal structural and functional findings in the reward network in relation to OW/OB in BD, we examined for differences in CBF in reward-related regions across 3 youth groups: OW/OB BD (BD_{OW/OB}), normal weight BD (BD_{NW}), and NW healthy controls (HC). We hypothesized that significant differences across these groups would be explained primarily by differences between BD_{OW/OB} and HC, with BD_{NW} intermediate between these groups.

METHODS

Participants

A total 141 English-speaking youth participants (58% female, 68% Caucasian), ages 13–20 years, were recruited to this study (25 BD_{OW/OB}, 55 BD_{NW}, 61 HC). BD participants who met criteria for BD-I, BD-II, or BD-not otherwise specified were recruited from a subspecialty clinic at Sunnybrook Health Sciences Centre in Toronto, Ontario. HC participants with no lifetime mood or psychiatric disorders and no first- or second-degree family history of BD or psychotic disorder were recruited from the community. Participants were excluded if they were unable to provide written informed consent or had cardiac, autoimmune, or

inflammatory illness, neurological or cognitive impairment, or contraindications to MRI. The current sample overlaps, in part, with previous studies on the BD-BMI link (MacIntosh et al., 2017; Islam et al., 2018; Karthikeyan et al., 2019). All participants and their parent/guardian(s) provided written informed consent. All procedures were performed at Sunnybrook Health Sciences Centre and were approved by the local research ethics board.

Clinical Procedures and Measures

Psychiatric diagnoses were confirmed using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version (Kaufman et al., 1997). Current and lifetime symptoms of depression and mania were assessed using the KSADS Depression Rating scale and KSADS Mania Rating Scale. Current mood was defined by depression and mania scores from the worst week in the past month. All diagnoses were made in compliance with the DSM-IV because this sample was recruited from 2012 through 2019 and the DSM-5 version of Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version was not available until December 2016 (Kaufman et al., 1997).

BMI was calculated as weight in kilograms (measured with a Tanita scale) divided by height in squared meters (measured using a stadiometer) and adjusted for clothing (−1.3 kg for long items; −1.1 kg if 1 item was short; −0.9 kg if both items were short) (Shapiro et al., 2017). Normal weight was defined as BMI < 25 and OW/OB was defined as BMI > 25. All HC were normal weight.

MRI Acquisition

Brain images were acquired using a 3-Tesla Philips Achieva scanner with an 8-channel head receiver coil. High resolution T1-weighted images were obtained for anatomical registration, and PC-ASL images were collected to derive CBF measures. Structural scans were acquired using fast-field echo imaging with the following parameters: repetition time (TR) 9.5 milliseconds, echo time (TE) 2.3 milliseconds, inversion time (TI) 1400 milliseconds, flip angle of 8 degrees, field of view 240 mm × 191 mm, spatial resolution 0.94 × 1.17 × 1.2 mm, 256 × 164 × 140 matrix, scan duration 8:56 min:s. Prior to ASL imaging, phase contrast

angiography scout images were acquired to visualize vascular anatomy. ASL images were obtained with single-shot 2-dimensional echo planar imaging with the following parameters: TR 4000 milliseconds, TE 9.7 milliseconds, 64 × 64 × 18 matrix, spatial resolution 3 × 3 × 5 mm, 1650-millisecond labeling duration, 1600-millisecond post-label delay for the most inferior slice, 30 control-tag pairs, and scan duration of 4:08 min:s. ASL reference images were acquired with TR 10 seconds to establish initial magnetization for CBF quantification.

Image Processing

Images were processed using FMRIB Software Library (FSL) tools. T1-weighted images were skull-stripped, co-registered to ASL space and standard space, normalized, and segmented into GM and WM. ASL images were co-registered to a reference volume. CBF was then estimated from differences in consecutive control and tag images. Images with excess head motion were identified automatically and removed to optimize CBF image quality. Estimates were converted to absolute units (mL/100 g/min), and CBF maps were smoothed with 5 mm full-width-half-maximum kernel. Regional CBF values were also extracted from masks of the ACC and the amygdala, which were defined using the Harvard-Oxford Cortical and subcortical Structural Atlases in FSL in 2 mm standard space.

Statistical Analysis

Normality of continuous demographic and clinical variables was assessed using the Shapiro-Wilk test. Three-way comparison of demographic characteristics and within BD analysis of clinical characteristics were performed in SPSS Version 26. Normally distributed data were analyzed using independent samples t tests or ANOVA (for 3 group comparisons). Nonparametric tests (Mann-Whitney U-tests and Kruskal-Wallis) were applied for variables not normally distributed. Categorical variables were analyzed using chi-squared (χ^2) tests. Tests were 2-tailed and used an a priori significance threshold of $P < .05$. Both a priori and exploratory approaches were taken to assess CBF differences between the 3 groups. A general linear model was used in SPSS to evaluate group differences in region of interest (ROI) CBF. Bonferroni correction was used to set the statistical significance

Table 1. Demographic Characteristics of Study Groups

	BDOW/OB (n=25)	BDNW (n=55)	HC (n=61)	Test Statistic	P	Effect Size
Age	17.32 ± 1.27	17.32 ± 1.45	16.73 ± 1.77	F = 2.40	.09	$\eta^2 = 0.03$
Sex (% female)	16 (64)	35 (64)	32 (53)	$\chi^2 = 1.82$.40	V = 0.11
SES	4.16 ± 1.03	4.27 ± 0.85	4.33 ± 0.96	H = 0.79	.67	$\eta^2 = 0.01$
Race (% Caucasian)	14 (56) ^a	46 (84) ^b	36 (59) ^a	$\chi^2 = 10.11$.006	V = 0.27
Intact family (%)	15(60)	33(60)	38(62)	$\chi^2 = 0.08$.96	V = 0.02
Tanner stage (1–5)	4.56 ± 0.65	4.38 ± 0.62	4.18 ± 0.67	H = 6.89	.03	$\eta^2 = 0.04$
BMI (adjusted)	29.1 ± 3.94 ^b	21.6 ± 1.99 ^a	20.6 ± 1.87 ^a	H = 65.86	<.001	$\eta^2 = 0.45$
BMI percentile ^c	92.55 ± 1.19 ^b	52.75 ± 3.10 ^a	46.34 ± 3.06 ^a	H = 56.73	<.001	$\eta^2 = 0.40$
Waist circumference ^c	89.89 ± 7.93 ^b	74.36 ± 6.47 ^a	72.66 ± 6.07 ^a	H = 46.58	<.001	$\eta^2 = 0.35$
CGAS – Most severe past	43.84 ± 9.05	43.48 ± 8.72	—	U = 660	.87	d = 0.04
CGAS – Past month ^d	66.80 ± 9.15 ^b	68.87 ± 11.99 ^b	88.34 ± 6.44 ^a	F = 95.41	<.001	$\eta^2 = 0.54$
CGAS – Current ^d	62.52 ± 11.42 ^b	64.94 ± 12.49 ^b	88.36 ± 6.11 ^a	F = 118.16	<.001	$\eta^2 = 0.60$

Abbreviations: BMI = body mass index; CGAS = Children's Global Assessment Scale; SES = socio-economic status. Values are reported in mean ± standard deviation unless otherwise specified.

^{a,b} Different superscripts denote a significant difference between different groups at $P = .05$.

^c Missing data points: BMI percentile-2 BD_{OW/OB}, 4 BD_{NW}, 5 HC; waist circumference- 3 BD_{OW/OB}, 6 BD_{NW}, 3 HC.

^d Homogeneity of variance violated, Welch test reported.

Table 2. Clinical Characteristics of BD_{NW} and BD_{OW/OB} Groups

	BD _{NW} (n=55)	BD _{OW/OB} (n=25)	Test Statistic	P value	Effect Size
BD-I (%)	22 (40)	8(32)	$\chi^2=0.57$		
BD-II (%)	14 (25)	8(32)		.75	V=0.09
BD-NOS (%)	19 (35)	9 (36)			
Age of onset	15.04±2.54	14.65±2.30	U=592.50	.32	d=0.16
Clinical characteristics					
Lifetime psychosis (%)	6 (11)	4(16)	$\chi^2=0.41$.72 ^a	V=0.07
Lifetime suicide attempts (%)	8 (15)	5(20)	$\chi^2=0.38$.53 ^a	V=0.07
Lifetime self-injurious behavior (%)	26(47)	14(56)	$\chi^2=0.52$.47	V=0.08
Lifetime suicidal ideation (%)	35 (64)	14(56)	$\chi^2=0.42$.52	V=0.07
Police contact/arrest (%)	15(27)	2(8)	$\chi^2=3.82$.051	V=0.22
Lifetime physical and/or sexual abuse (%)	5(9)	0(0)	$\chi^2=2.42$.32 ^a	V=0.17
Lifetime psychiatric hospitalization (%)	28 (51)	10(40)	$\chi^2=0.82$.37	V=0.10
Current depression score	14.58±10.91	18.28±12.45	U=798.00	.25	d=0.32
Lifetime depression score	29.49±12.65	30.80±11.60	U=704.00	.86	d=0.11
Current mania score	9.35±10.30	10.12±10.57	U=708.50	.82	d=0.07
Lifetime mania score	30.71±9.89	32.52±12.22	t=-0.70	.48	d=0.16
Lifetime comorbid diagnoses					
ADHD (%)	26(47)	10(40)	$\chi^2=0.37$.54	V=0.07
Any anxiety (%)	41 (75)	21(84)	$\chi^2=0.88$.35	V=0.11
ODD (%)	9(16)	11(44)	$\chi^2=7.00$.008	V=0.30
CD (%)	2 (4)	1(4)	$\chi^2=0.006$	>.99 ^a	V=0.01
Nicotine use (yes/no) (%)	7 (13)	4(16)	$\chi^2=0.16$.73 ^a	V=0.04
Any SUD	12 (22)	6 (24)	$\chi^2=0.05$	>.99	V=0.02
Anorexia nervosa (%)	1 (2)	1 (4)	$\chi^2=0.34$.53 ^a	V=0.65
Bulimia nervosa (%)	3 (5)	2 (8)	$\chi^2=0.19$.65 ^a	V=0.05
Eating disorder-NOS (%)	12 (22)	6 (24)	$\chi^2=0.05$.83	V=0.02
Family psychiatric history					
Mania/hypomania (%)	26(47)	12(48)	$\chi^2=0.004$.95	V=0.01
Depression (%)	39 (71)	18(72)	$\chi^2=0.01$.92	V=0.01
Anxiety (%)	31(56)	17(68)	$\chi^2=0.97$.33	V=0.11
ADHD (%)	18 (33)	6(24)	$\chi^2=0.62$.43	V=0.09
Lifetime medications					
SGA (%)	42 (76)	17 (68)	$\chi^2=0.62$.43	V=0.09
Lithium (%)	13 (24)	7 (28)	$\chi^2=0.18$.68	V=0.05
SSRI antidepressants (%)	15(27)	10(40)	$\chi^2=1.30$.26	V=0.13
Non-SSRI antidepressants (%)	10 (18)	6(24)	$\chi^2=0.36$.55	V=0.07
Stimulants (%)	12 (22)	4 (16)	$\chi^2=0.36$.55	V=0.07
Current medications					
SGA (%)	35 (64)	13 (52)	$\chi^2=0.97$.33	V=0.11
Lithium (%)	8 (15)	7 (28)	$\chi^2=2.04$.22 ^a	V=0.16
SSRI antidepressants (%)	3(5)	4 (16)	$\chi^2=2.39$.20 ^a	V=0.17
Non-SSRI antidepressants (%)	2 (4)	2(8)	$\chi^2=0.69$.59 ^a	V=0.09
Stimulants (%)	5 (9)	0 (0)	$\chi^2=2.42$.32 ^a	V=0.17

Abbreviations: ADHD, attention deficit-hyperactivity disorder; CD, conduct disorder; NOS, not otherwise specified; ODD, oppositional defiant disorder; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; SUD, substance use disorder.

Values are mean±SD unless otherwise indicated.

^a P value reported from Fisher's Exact Test. Depression score based on depression rating scale. Mania score based on mania rating scale.

Table 3. Mean Global and Regional Cerebral Blood Flow Across Groups

Mean CBF	BD _{OW/OB} (n=25)	BD _{NW} (n=55)	HC (n=61)	Statistics		
				F	Partial η^2	P
Global Gray Matter	63.63 (9.84)	66.75 (13.21)	63.58 (11.43)	1.18	0.02	.31
ACC	72.82 (9.93)	76.14 (16.77)	72.25 (14.89)	1.06	0.02	.35
Amygdala	42.58 (8.59)	43.86 (10.71)	41.21 (11.14)	0.91	0.01	.41

Abbreviations: ACC, anterior cingulate cortex; BD, bipolar disorder; CBF, cerebral blood flow; HC, healthy controls.

CBF values are reported in mL/100 g/min (mean±SD). ACC and amygdala CBF values were extracted from masks restricted to GM voxels. Unadjusted P values are reported.

threshold to $P=.017$ to control for the 3 ROIs. CBF group differences were also assessed using a whole-brain voxel-wise approach. A general linear model was designed in FSL using the FMRIB's Local Analysis of Mixed Effects (FLAME1). Three group contrast CBF maps corresponding to pair-wise comparisons between BD_{NW} and BD_{OW} , BD_{NW} and HC, as well as BD_{OW} and HC were corrected using FSL cluster, a multiple comparisons correction method that controls family wise error rate. Specifically, a cluster-forming threshold of $z=2.4$, corresponding to $P=.017$ to account for the number of group comparisons, and a secondary threshold of $P=.05$ to determine cluster significance were specified. Given the association of second-generation antipsychotics with BMI and OW/OB, sensitivity analyses controlling for this variable were also undertaken.

RESULTS

Demographic and Clinical Characteristics

Demographic characteristics are summarized in Table 1. There were no significant between-group differences in age or sex. By definition, BMI and WC were significantly higher in the $BD_{OW/OB}$ group ($P<.001$; 29.1 ± 3.94 kg/m² and 89.9 ± 7.93 , respectively) compared with the BD_{NW} (21.6 ± 1.99 kg/m² and 74.4 ± 6.47 , respectively) and HC groups (20.6 ± 1.87 kg/m² and 72.66 ± 6.07 , respectively), whereas BD_{NW} and HC did not differ significantly. Clinical characteristics for youth with BD are presented in Table 2. $BD_{OW/OB}$ showed more cases of oppositional defiant disorder compared with BD_{NW} ($P=.008$). Groups did not differ in terms of current mania/depression. In terms of the HC group, 1 participant had current SSRI antidepressants, and 3 participants had current stimulant use.

ROI CBF Analysis

Group means for ROI CBF are presented in Table 3 and Figure 1. There were no significant between-group ROI differences (amygdala, $P=.09$; ACC, $P=.18$).

Voxel-Wise CBF Analysis

In the voxel-wise analysis, the BD_{NW} group had significantly higher CBF than the HC group ($P<.017$, $\eta^2=0.10$) in the basal ganglia (with a peak signal in the putamen), nucleus accumbens, and PFC (Table 4; Figure 2). Similarly, the BD_{NW} group had significantly higher CBF relative to the $BD_{OW/OB}$ group ($P<.017$, $\eta^2=0.14$), with a peak signal in the pallidum extending into to the putamen and thalamus (Table 4; Figure 3).

Sensitivity Analysis

A sensitivity analysis was undertaken for both ROI and voxel-wise CBF results covarying for current second-generation antipsychotic use. In the ROI analysis, ANCOVA findings were unchanged. In the voxel-wise analysis, the aforementioned findings remained significant, and there were 2 additional significant occipital clusters.

DISCUSSION

In this study, we investigated BMI, in part a reward-related phenotype, in relation to reward circuit regional CBF in youth early in their course of BD. ROI analyses focusing on ACC and amygdala revealed no significant differences between groups. In voxel-wise analyses, contrary to our hypothesis, we found higher regional CBF among BD_{NW} in the basal ganglia, NAc, and PFC compared with NW HC, and in pallidum extending into to the putamen and thalamus compared with $BD_{OW/OB}$. This study addresses a gap in the literature regarding CBF in relation to obesity or BMI among individuals with BD, a population in whom obesity is common and correlates with adverse clinical characteristics.

The regions identified in voxel-wise analyses are all involved in reward processing. Abnormalities in key regions of the dopamine reward system, including the basal ganglia, NAc, thalamus, and PFC, have been associated with mood episodes in BD (Trost et al., 2014). The caudate and putamen, which make up

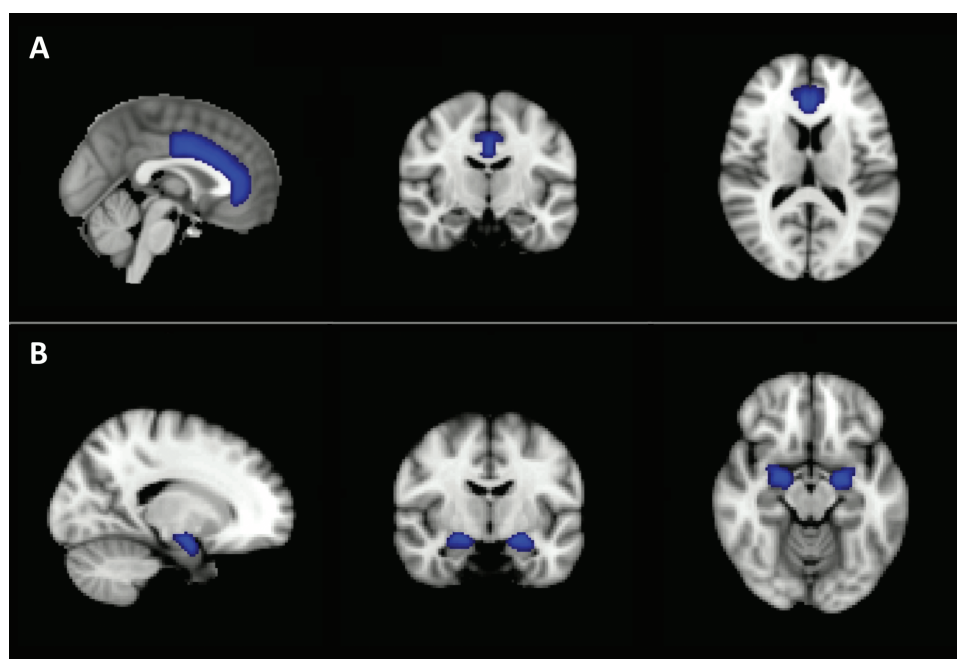


Figure 1. Region of interest (ROI) masks are overlaid on a 2-mm standard brain. (A) Cerebral blood flow (CBF) estimates in the anterior cingulate cortex (ACC) were 72.82 ± 9.93 for $BD_{OW/OB}$, 76.14 ± 16.77 for BD_{NW} , and 72.25 ± 14.89 mL/100 g/min for HC. (B) CBF estimates in the amygdala were 42.58 ± 8.59 for $BD_{OW/OB}$, 43.86 ± 10.71 for BD_{NW} , and 41.21 ± 11.14 for HC. Abbreviations: $BD_{OW/OB}$, BD with comorbid overweight/obesity; BD_{NW} , BD with normal weight.

Table 4. Significant Clusters from Voxel-Wise z-stat Contrast Maps

Contrast	Cluster size (voxels)	Peak signal MNI coordinates (X, Y, Z)			Regions
BD _{NW} >HC	453	-21	21	-9	Putamen (peak), caudate, pallidum, nucleus accumbens, frontal orbital cortex, insular cortex
BD _{NW} >BD _{OW/OB}	167	-18	-3	0	Pallidum (peak), thalamus, putamen

Abbreviations: BD, bipolar disorder; HC, healthy controls; MNI, Montreal Neurological Institute.

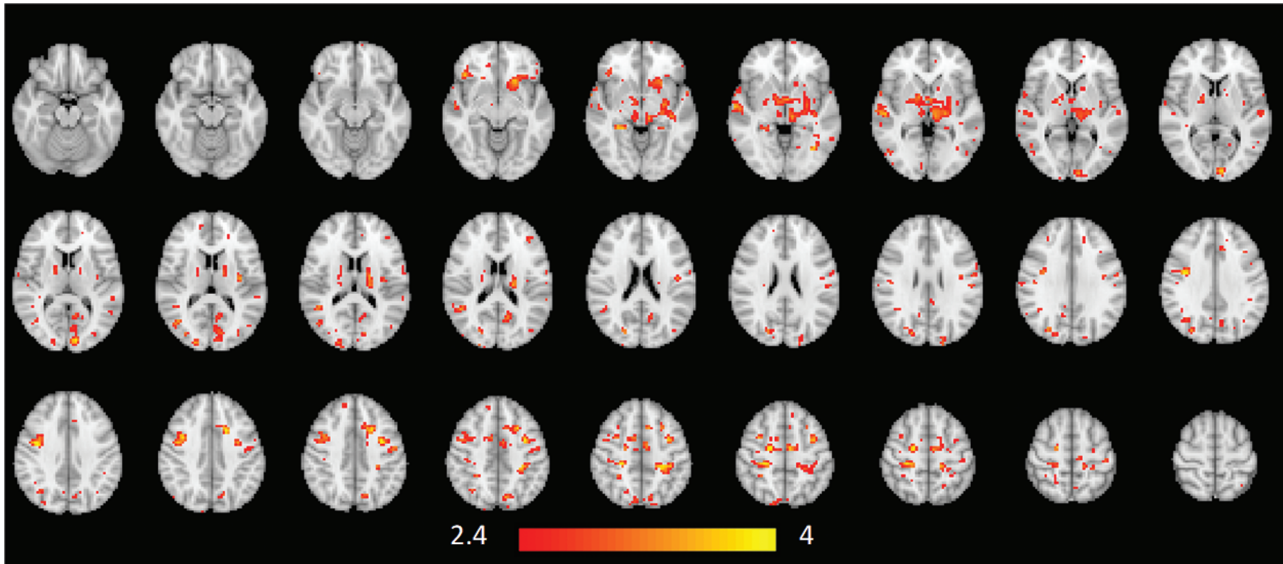


Figure 2. Cluster-corrected Z-statistics image ($z=2.4$, secondary threshold of $P=.05$) overlaid onto a standard structural image. The red to yellow color scale displays regions in which CBF is higher for normal weight BD compared with healthy controls.

the dorsal striatum, are involved in addictive behavior as shown by the increased metabolic activity and dopamine release from these regions following cue-induced craving (Taylor et al., 2013). The NAC, part of the ventral striatum, integrates reward-related information and promotes both motivation and aversion (Hikida et al., 2016).

Higher CBF in reward-related regions found in BD_{NW} vs HC overlap with regions for which there is evidence of resting state functional connectivity anomalies during mood episodes (Selvaraj et al., 2012). Hypo/mania is associated with increased connectivity of the caudate to the thalamus and dopamine-rich substantia nigra, which may reflect the increased motivation and reward-seeking behavior in the elevated mood state (Selvaraj et al., 2012). In adults with bipolar depression, there is increased connectivity of the putamen with somatosensory areas such as the insula and temporal gyrus, which may reflect altered emotional interpretation of negative thoughts as demonstrated by the increased prominence of internal and external negative events in depression (Altinay et al., 2016).

Task-based fMRI studies have inconsistently implicated anomalous fronto-striatal reward-related regions in BD (Nusslock et al., 2014). Although BD is often characterized by elevated striatal, OFC, and amygdala neural activation—as demonstrated in the response to positive stimuli during both mania and euthymia (Elliott et al., 2004; Hassel et al., 2008; Bermpohl et al., 2009)—there is also evidence of decreased activation of the ventral ACC, OFC, and ventral striatum in response to happy and emotionally neutral stimuli across various mood states (hypo/manic, mixed, depressed) and euthymia (Liu et al.,

2012). In addition, lateralized abnormalities have been reported, including diminished right PFC response to fearful and neutral stimuli in elevated states and increased left OFC response to fearful stimuli in depressed states (Liu et al., 2012).

Individuals with obesity show heightened sensitivity of the reward circuitry, specifically the dorsal striatum and NAC, to high-calorie food stimuli but decreased sensitivity to the rewarding effects of food consumption (Volkow et al., 2011). This is associated with weakened PFC-regulated inhibitory control over appetitive behavior and promotes compulsive eating (Volkow et al., 2011; Gluck et al., 2017). Related to our current findings, we previously found that waist circumference was associated with reward impulsivity in youth with BD, demonstrating a potential cardiovascular-cognitive link in this age group (Naiberg et al., 2016). We speculate that the basal ganglia and thalamus may have greater perfusion demands in BD such that the pattern of similar CBF in these regions in BD_{OW/OB} vs HC and lower CBF in BD_{OW/OB} vs BD_{NW} may reflect a compensatory failure to increase CBF in the BD_{OW/OB} group. The current cross-sectional study cannot address directionality; as such, it is not clear whether OW/OB interferes with compensatory increases in CBF or whether failure of a compensatory mechanism contributes to OW/OB.

Several limitations must be addressed on interpretation of our findings. First, although the sample is comparatively large for a neuroimaging study in this area, the BD_{OW/OB} subgroup was meaningfully smaller than the other subgroups. We also did not examine HC with OW/OB, who have been shown to have lower CBF compared with individuals with normal weight (Volkow et al., 2010; Willeumier et al., 2011; Peng and Chen, 2020). Second,

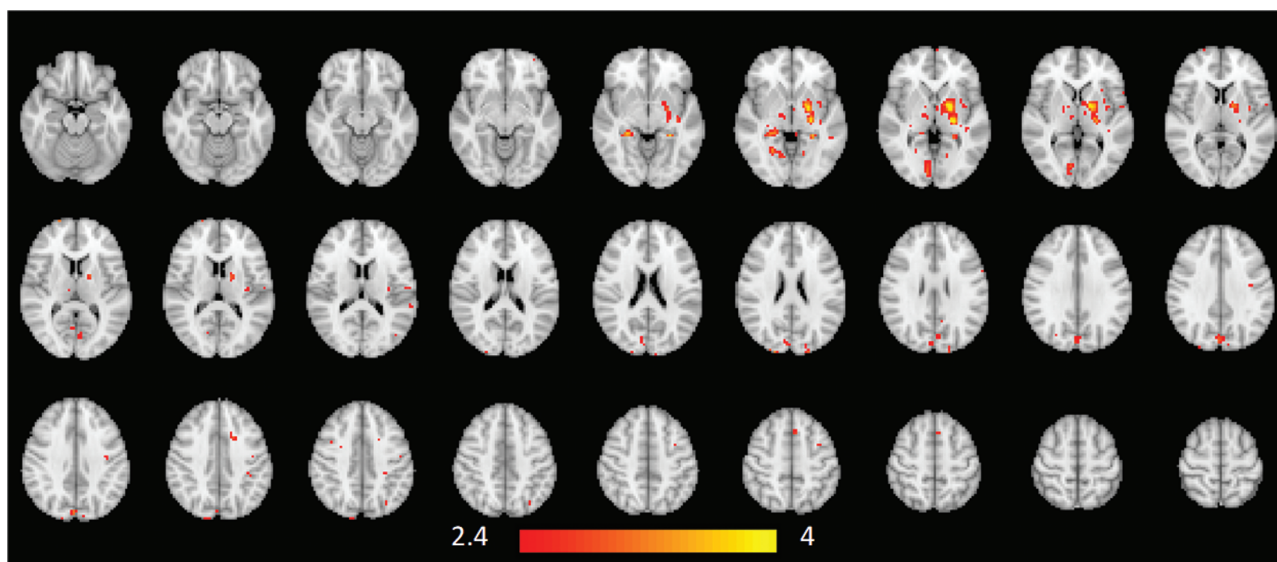


Figure 3. Cluster-corrected Z-statistics image ($z=2.4$, secondary threshold of $P=.05$) overlaid onto a standard structural image. The red to yellow color scale displays regions in which CBF is higher for normal weight BD compared with overweight/obese BD.

as previously acknowledged, the cross-sectional design of this study precludes inferences regarding the direction of the observed associations, and the study did not include measures that can inform our understanding of the mechanisms underlying these associations. Third, as is expected based on the epidemiology of BD, our BD sample was heterogeneous, including different BD subtypes, comorbidities, family psychiatric history, and medications (Phillips and Swartz, 2014). As shown by our sensitivity analyses, no meaningful changes in findings were observed after adjusting for current second-generation antipsychotic use. Finally, the study did not include a reward-related task, which may have been more sensitive to OW/OB-related differences in CBF.

This study provides initial evidence of increased CBF in reward circuits and other BD-related brain regions in BD_{NW} compared with both $BD_{OW/OB}$ and HC. We speculate that these differences may reflect a compensatory mechanism, potentially related to anomalous oxidative and/or glucose metabolism. Longitudinal studies with larger samples of $BD_{OW/OB}$ are warranted to assess directionality of CBF changes in BD in relation to BMI and other indicators of OW/OB. Relatedly, intervention studies have the potential to elucidate how changes in BMI can affect CBF levels and related adverse clinical characteristics. Finally, studies examining this topic across the lifespan could inform our understanding of developmental differences in the association between CBF and OW/OB in BD.

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Interest Statement

The authors certify that they have no financial interest to disclose.

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