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

Anahit Grigorian¹; Kody G Kennedy¹,²; Nicholas J Luciw³; Bradley J MacIntosh³,⁴,⁵; Benjamin I Goldstein¹,²,⁵,⁶*

¹ Centre for Youth Bipolar Disorder, Department of Child and Youth Psychiatry, Centre for Addiction and Mental Health, Toronto, Ontario
² Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario
³ Department of Medical Biophysics, University of Toronto, Toronto, Ontario
⁴ Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, Ontario
⁵ Hurvitz Brain Sciences, Sunnybrook Research Institute, Toronto, Ontario
⁶ Department of Psychiatry, University of Toronto, Toronto, Ontario

* Correspondence:
Dr. Benjamin I. Goldstein
Centre for Addiction and Mental Health
80 Workman Way
Toronto, ON, Canada, M6J 1H4
Phone: 416-535-8501 ext. 39129
Email: benjamin.goldstein@camh.ca

Abstract Paper Category: Regular Research Article
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 to 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.
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 3T magnetic resonance imaging (MRI). CBF differences were assessed using both region of interest (ROI) 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 ROI 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
List of Acronyms: ACC= anterior cingulate cortex; ANCOVA= analysis of covariance; ANOVA= analysis of variance; ASL= arterial spin labeling; BD= bipolar disorder; BMI= body mass index; CBF= cerebral blood flow; DEP-P= Depression Rating scale; DMN= default mode network; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FLAME1= FMRIB’s Local Analysis of Mixed Effects; FSL= FMRIB Software Library; GLM= general linear model; GM= gray matter; HC= healthy controls; K-SADS-PL= Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version; MRI= magnetic resonance imaging; MRS= Mania Rating Scale; NAc= nucleus accumbens; NOS= not otherwise specified; NW= normal weight; OFC= orbitofrontal cortex; OW/OB= overweight/obese; (PC) ASL= pseudo-continuous ASL; PFC= prefrontal cortex; ROI= region of interest; rsFC= resting state functional connectivity; SN= salience network; SPSS= statistical package for the social sciences; TE= echo time; TI= inversion time; TR= repetition time; WM= white matter
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 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 (rsFC) studies have predominantly linked higher BMI to disrupted connectivity between key regions of the salience network (SN; e.g. nucleus accumbens (NAc), amygdala, dorsal striatum) and the default mode network (DMN; 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/100g/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 use arterial spin labeling (ASL) to investigate the relationship between CBF and BMI. Unlike nuclear medicine methods that use exogenous radioactive tracers, ASL is a non-invasive 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 three 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

One hundred and forty-one 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 (NOS) 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, 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 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 (K-SADS-PL) (Kaufman et al., 1997). Current and lifetime symptoms of depression and mania were assessed using the KSADS Depression Rating scale (DEP-P) and KSADS Mania Rating Scale (MRS). 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 Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria (DSM-IV), as this sample was recruited from 2012 through 2019 and the DSM-5 version of K-SADS-PL 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 one 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 (3T) 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 ms, echo time (TE) 2.3 ms, inversion time (TI) 1400 ms, 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 two-dimensional EPI with the following parameters: TR 4000 ms, TE 9.7 ms, 64×64×18 matrix, spatial resolution 3×3×5 mm, 1650 ms labeling duration, 1600 ms post-label delay for the most inferior slice, 30 control-tag pairs, scan duration of 4:08 min:s. ASL reference images were acquired with TR 10 s to establish initial magnetization for CBF quantification.
Image processing

Image 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 grey and white matter. 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/100g/min), and CBF maps were smoothed with 5mm 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 2mm 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 analysis of variance (ANOVA, for 3 group comparisons). Non-parametric tests (Mann-Whitney U-tests and Kruskal-Wallis) were applied for variables that were not normally distributed. Categorical variables were analyzed using chi-squared (χ2) tests. Tests were two-tailed and used an a priori significance threshold of p<0.05. Both a priori and exploratory approaches were taken to assess CBF differences between the three groups. A general linear model (GLM) was used in SPSS to evaluate group differences in region of interest (ROI) CBF. Bonferroni correction was used to set the statistical significance threshold to p= 0.017 to control for the three ROIs. CBF group differences were also assessed using a whole brain voxel-wise approach. A GLM 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 (FWER). Specifically, a cluster-forming threshold of z=2.4,
corresponding to $p=0.017$ to account for the number of group comparisons, and a secondary threshold of $p=0.05$ 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 ($p<0.001$; $29.1 \pm 3.94 \text{ kg/m}^2$ and $89.9 \pm 7.93$, respectively) compared to the $BD_{NW}$ ($21.6 \pm 1.99 \text{ kg/m}^2$ and $74.4 \pm 6.47$, respectively) and HC groups ($20.6 \pm 1.87 \text{ kg/m}^2$ and $72.66 \pm 6.07$, 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 to $BD_{NW}$ ($p=0.008$). Groups did not differ in terms of current mania/depression. In terms of the HC group, one participant had current SSRI antidepressants, and three participants had current stimulant use.

*Region of interest CBF analysis*

Group means for ROI CBF are presented in Table 3 and Figure 1. There were no significant between-group ROI differences (amygdala, $p=0.09$; ACC, $p=0.18$).

*Voxel-wise CBF analysis*

In the voxel-wise analysis, the $BD_{NW}$ group had significantly higher CBF than the HC group ($p<0.017$, $\eta^2=0.10$) 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 ($p<0.017$, $\eta^2=0.14$), with a peak signal in the pallidum extending into 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 two 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. Region of interest 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 to NW HC, and in pallidum extending into to the putamen and thalamus compared to 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 that were 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 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\textsubscript{OW/OB} vs. HC and lower CBF in BD\textsubscript{OW/OB} vs. BD\textsubscript{NW} may reflect a compensatory failure to increase CBF in the BD\textsubscript{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 upon interpretation of our findings. First, although the sample is comparatively large for a neuroimaging study in this area, the BD\textsubscript{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 to individuals with normal weight (Volkow et al., 2010; Willeumier et al., 2011; Peng and Chen, 2020). Second, 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 to 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.
Funding

This study was funded by the Ontario Mental Health Foundation (grant number 1010589) and the Canadian Institute of Health Research (CIHR; grant number MOP-136947).

Acknowledgements

B.I. Goldstein is supported by the RBC Investments Chair in Children’s Mental Health and Developmental Psychopathology at CAMH, a joint Hospital-University Chair between the University of Toronto, CAMH, and the CAMH Foundation. Dr. B. I. Goldstein has received research support from the Brain and Behavior Research Foundation (NARSAD), Brain Canada, CIHR, the Heart and Stroke Foundation, National Institute of Mental Health, and the departments of psychiatry of Sunnybrook Health Sciences Centre and the University of Toronto. B. J. MacIntosh receives grant or research support from the CIHR, Natural Sciences and Engineering Research Council, and NARSAD. The authors would like to thank the staff and graduate students at the Centre for Youth Bipolar Disorder for their contribution, and youth and their families for their participation.

Statement of Interest

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

Alosco ML, Stanek KM, Galioto R, Korgaonkar MS, Grieve SM, Brickman AM, Spitznagel MB, Gunstad J (2014) Body mass index and brain structure in healthy children and adolescents. Int J Neurosci 124:49–55.

Altinay MI, Hulvershorn LA, Karne H, Beall EB, Anand A (2016) Differential Resting-State Functional Connectivity of Striatal Subregions in Bipolar Depression and Hypomania. Brain Connect 6:255–265.

Arjmand S, Behzadi M, Stephens GJ, Ezzatabadipour S, Seifaddini R, Arjmand S, Shabani M (2018) A Brain on a Roller Coaster: Can the Dopamine Reward System Act as a Protagonist to Subdue the Ups and Downs of Bipolar Disorder? Neuroscientist 24:423–439.

Bauer CCC, Moreno B, González-Santos L, Concha L, Barquera S, Barrios FA (2015) Child overweight and obesity are associated with reduced executive cognitive performance and brain alterations: A magnetic resonance imaging study in Mexican children. Pediatr Obes 10:196–204.

Bermpohl F, Dalanay U, Kahnt T, Sajonz B, Heimann H, Ricken R, Stoy M, Hägele C, Schlagenauf F, Adli M, Wrase J, Ströhle A, Heinz A, Bauer M (2009) A preliminary study of increased amygdala activation to positive affective stimuli in mania. Bipolar Disord 11:70–75.

Black WR, Lepping RJ, Bruce AS, Powell JN, Bruce JM, Martin LE, Davis AM, Brooks WM, Savage CR, Simmons WK (2014) Tonic hyper-connectivity of reward neurocircuitry in obese children. Obesity 22:1590–1593.

Bond DJ, Ha TH, Lang DJ, Su W, Torres IJ, Honer WG, Lam RW, Yatham LN (2014) Body mass index-related regional gray and white matter volume reductions in first-episode mania patients. Biol Psychiatry 76:138–145.
Bond DJ, Lang DJ, Noronha MM, Kunz M, Torres IJ, Su W, Honer WG, Lam RW, Yatham LN (2011) The association of elevated body mass index with reduced brain volumes in first-episode mania. Biol Psychiatry 70:381–387.

Chodkowski BAA, Cowan RL, Niswender KD (2016) Imbalance in resting state functional connectivity is associated with eating behaviors and adiposity in children. Heliyon 2.

Chugani HT, Phelps ME, Mazziotta JC (1987) Positron emission tomography study of human brain functional development. Ann Neurol 22:487–497.

Contreras-Rodríguez O, Martín-Pérez C, Vilar-López R, Verdejo-Garcia A (2017) Ventral and Dorsal Striatum Networks in Obesity: Link to Food Craving and Weight Gain. Biol Psychiatry 81:789–796.

Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ (2004) Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. Biol Psychiatry 55:1163–1170.

Fagiolini A, Kupfer DJ, Rucci P, Scott JA, Novick DM, Frank E (2004) Suicide attempts and ideation in patients with bipolar I disorder. J Clin Psychiatry 65:509–514.

Fantini S, Sassaroli A, Tgavalekos KT, Kornbluth J (2016) Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. Neurophotonics 3:031411.

Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR, Bent EK, Koneru VK, Dieterich ME, Hodge SM, Rauch SL, Grant PE, Cohen BM, Seidman LJ, Caviness VS, Biederman J (2005) Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 162:1256–1265.

Giedd JN, Blumenthal J, Jeffries J, Castellanos EX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapaport JL
(1999) Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 10:861–863.

Gluck ME, Viswanath P, Stinson EJ (2017) Obesity, Appetite, and the Prefrontal Cortex. Curr Obes Rep 6:380–388.

Goldstein BI, Birmaher B, Axelson DA, Goldstein TR, Esposito-Smythers C, Strober MA, Hunt J, Leonard H, Gill MK, Iyengar S, Grimm C, Yang M, Ryan ND, Keller MB (2008) Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. J Clin Psychiatry 69:1953–1959.

Goldstein BI, Blanco C, He JP, Merikangas K (2016) Correlates of Overweight and Obesity Among Adolescents With Bipolar Disorder in the National Comorbidity Survey–Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry 55:1020–1026.

Goldstein BI, Liu SM, Schaffer A, Sala R, Blanco C (2013) Obesity and the three-year longitudinal course of bipolar disorder. Bipolar Disord 15:284–293.

Goldstein BI, Liu SM, Zivkovic N, Schaffer A, Chien LC, Blanco C (2011) The burden of obesity among adults with bipolar disorder in the United States. Bipolar Disord 13:387–395.

Hassel S, Almeida RJ, Kerr N, Nau S, Ladouceur DC, Fissell K, Kupfer DJ, Phillips ML (2008) Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. Bipolar Disord 10:916–927.

Hikida T, Morita M, Macpherson T (2016) Neural mechanisms of the nucleus accumbens circuit in reward and aversive learning. Neurosci Res 108:1–5.

Hogenkamp PS, Zhou W, Dahlberg LS, Stark J, Larsen AL, Olivo G, Wiemerslage L, Larsson EM, Sundbom M, Benedict C, Schiöth HB (2016) Higher resting-state activity in reward-related brain...
circuits in obese versus normal-weight females independent of food intake. Int J Obes 40:1687–1692.

Islam AH, Metcalfe AWS, Macintosh BJ, Korczak DJ, Goldstein BI (2018) Greater body mass index is associated with reduced frontal cortical volumes among adolescents with bipolar disorder. J Psychiatry Neurosci 43:120–130.

Jennings JR, Heim AF, Kuan DCH, Gianaros PJ, Muldoon MF, Manuck SB (2013) Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. Stroke 44:2480–2485.

Karthikeyan S, Fiksenbaum L, Grigorian A, Lu H, Macintosh BJ, Goldstein BI (2019) Normal Cerebral Oxygen Consumption Despite Elevated Cerebral Blood Flow in Adolescents With Bipolar Disorder: Putative Neuroimaging Evidence of Anomalous Energy Metabolism. Front Psychiatry 10.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988.

Kurth F, Levitt JG, Phillips OR, Luders E, Woods RP, Mazziotta JC, Toga AW, Narr KL (2013) Relationships between gray matter, body mass index, and waist circumference in healthy adults. Hum Brain Mapp 34:1737–1746.

Laurent JS, Watts R, Adise S, Allgaier N, Chaarani B, Garavan H, Potter A, Mackey S (2020) Associations among Body Mass Index, Cortical Thickness, and Executive Function in Children. JAMA Pediatr 174:170–177.

Liu J, Blond NB, van Dyck IL, Spencer L, Wang F, Blumberg PH (2012) Trait and state corticostriatal dysfunction in bipolar disorder during emotional face processing. Bipolar Disord 14:432–441.

Lopresti AL, Drummond PD (2013) Obesity and psychiatric disorders: Commonalities in dysregulated
biological pathways and their implications for treatment. Prog Neuro-Psychopharmacology Biol Psychiatry 45:92–99.

MacIntosh BJ, Shirzadi Z, Scavone A, Metcalfe AW, Islam AH, Korczak D, Goldstein BI (2017)
Increased cerebral blood flow among adolescents with bipolar disorder at rest is reduced following acute aerobic exercise. J Affect Disord 208:205–213.

Mazza E, Poletti S, Bollettini I, Locatelli C, Falini A, Colombo C, Benedetti F (2017) Body mass index associates with white matter microstructure in bipolar depression. Bipolar Disord 19:116–127.

McElroy SL, Keck PE (2012) Obesity in bipolar disorder: An overview. Curr Psychiatry Rep 14:650–658.

McIntyre RS, McElroy SL, Konarski JZ, Soczynska JK, Bottas A, Castel S, Wilkins K, Kennedy SH (2007) Substance use disorders and overweight/obesity in bipolar I disorder: Preliminary evidence for competing addictions. J Clin Psychiatry 68:1352–1357.

Meng Q, Han Y, Ji G, Li G, Hu Y, Liu L, Jin Q, von Deneen KM, Zhao J, Cui G, Wang H, Tomasi D, Volkow ND, Liu J, Nie Y, Zhang Y, Wang GJ (2018) Disrupted topological organization of the frontal-mesolimbic network in obese patients. Brain Imaging Behav 12:1544–1555.

Naiberg MR, Newton DF, Collins JE, Bowie CR, Goldstein BI (2016) Impulsivity is associated with blood pressure and waist circumference among adolescents with bipolar disorder. J Psychiatr Res 83:230–239.

Nusslock R, Young BC, Katherine D (2014) Elevated Reward-Related Neural Activation as a Unique Biological Marker of Bipolar Disorder: Assessment and Treatment Implications. Behav Reseach Ther 62:74–87.

Peng SL, Chen CM (2020) The influence of obesity on cerebral blood flow in young adults using arterial spin labeling MRI. NMR Biomed 33:1–8.
Pfeifer JC, Welge J, Strakowski SM, Adler CM, Delbello Department Of Psychiatry MP (2008) Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 47:1289–1298.

Phillips LM, Swartz AH (2014) A critical appraisal of neuroimaging studies of bipolar disorder: towards a new conceptualization of underlying neural circuitry and roadmap for future research. Am J Psychiatry 171:829–843.

Roberts G, Lord A, Frankland A, Wright A, Lau P, Levy F, Lenroot RK, Mitchell PB, Breakspear M (2017) Functional Dysconnection of the Inferior Frontal Gyrus in Young People With Bipolar Disorder or at Genetic High Risk. Biol Psychiatry 81:718–727.

Rosen HR, Rich BA (2010) Neurocognitive correlates of emotional stimulus processing in pediatric bipolar disorder: A review. Postgrad Med 122:94–104.

Satterthwaite TD, Kable JW, Vandekar L, Katchmar N, Bassett DS, Baldassano CF, Ruparel K, Elliott MA, Sheline YI, Gur RC, Gur RE, Davatzikos C, Leibenluft E, Thase ME, Wolf DH (2015) Common and Dissociable Dysfunction of the Reward System in Bipolar and Unipolar Depression. Neuropsychopharmacology 40:2258–2268.

Saute RL, Soder RB, Alves Filho JO, Baldisserotto M, Franco AR (2018) Increased brain cortical thickness associated with visceral fat in adolescents. Pediatr Obes 13:74–77.

Selvaraj S, Arnone D, Job D, Stanfield A, Farrow TFD, Nugent AC, Scherk H, Gruber O, Chen X, Sachdev PS, Dickstein DP, Malhi GS, Ha TH, Ha K, Phillips ML, McIntosh AM (2012) Grey matter differences in bipolar disorder: A meta-analysis of voxel-based morphometry studies. Bipolar Disord 14:135–145.

Shapiro J, Mindra S, Timmins V, Swampillai B, Scavone A, Collinger K, Collins J, Goldstein BI (2017) Controlled Study of Obesity among Adolescents with Bipolar Disorder. J Child Adolesc
Sharkey RJ, Karama S, Dagher A (2015) Overweight is not associated with cortical thickness alterations in children. Front Neurosci 9:1–7.

Sharma A, Wolf DH, Ciric R, Kable JW, Moore TM, Vandekar SN, Katchmar N, Daldal A, Ruparel K, Davatzikos C, Elliott MA, Calkins ME, Shinohara RT, Bassett DS, Satterthwaite TD (2017) Connectome-Wide Analysis Reveals Common Dimensional Reward Deficits Across Mood and Psychotic Disorders. Am J Psychiatry 174:657–666.

Shi J, Geng J, Yan R, Liu X, Chen Y, Zhu R, Wang X, Shao J, Bi K, Xiao M, Yao Z, Lu Q (2018) Differentiation of transformed bipolar disorder from unipolar depression by resting-state functional connectivity within reward circuit. Front Psychol 9:1–10.

Taylor BS, Lewis RC, Olive MF (2013) The neurocircuitry of illicit psychostimulant addiction: acute and chronic effects in humans. Subst Abuse Rehabil: 29.

Toma S, MacIntosh BJ, Swardfager W, Goldstein BI (2018) Cerebral blood flow in bipolar disorder: A systematic review. J Affect Disord 241:505–513.

Trost S, Diekhof EK, Zvonik K, Lewandowski M, Usher J, Keil M, Zilles D, Falkai P, Dechent P, Gruber O (2014) Disturbed anterior prefrontal control of the mesolimbic reward system and increased impulsivity in bipolar disorder. Neuropsychopharmacology 39:1914–1923.

Volkow DN, Wang G-J, Baler DR (2011) Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci 15:37–46.

Volkow ND, Wang G, Telang F, Fowler JS, Rita Z, Alia-klein N, Logan J, Wong C, Thanos PK (2010) Activity in Healthy Adults. Obesity 17:60–65.
Wang H, Wen B, Cheng J, Li H (2017) Brain structural differences between normal and obese adults and their links with lack of perseverance, negative urgency, and sensation seeking. Sci Rep 7:1–7.

Wei S, Geng H, Jiang X, Zhou Q, Chang M, Zhou Y, Xu K, Tang Y, Wang F (2017) Amygdala-prefrontal cortex resting-state functional connectivity varies with first depressive or manic episode in bipolar disorder. Neurosci Lett 641:51–55.

Willeumier KC, Taylor D V., Amen DG (2011) Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. Obesity 19:1095–1097.

Zhang P, Liu Y, Lv H, Li M yi, Yu F xia, Wang Z, Ding H yu, Wang L xue, Zhao K xin, Zhang Z yu, Zhao P fei, Li J, Yang Z han, Zhang Z tao, Wang Z chang (2019) Integration of Neural Reward Processing and Appetite-Related Signaling in Obese Females: Evidence From Resting-State fMRI. J Magn Reson Imaging 50:541–551.
**Figure 1:** ROI masks are overlaid on a 2mm standard brain. A) CBF estimates in the ACC were 72.82 ±9.93 for BD_{OW/OB}, 76.14 ±16.77 for BD_{NW}, and 72.25 ±14.89 mL/100g/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.

**Figure 2:** Cluster-corrected Z-statistics image (z=2.4, secondary threshold of p=0.05) overlaid onto a standard structural image. The red to yellow color scale displays regions in which CBF is higher for normal weight BD compared to healthy controls.

**Figure 3:** Cluster-corrected Z-statistics image (z=2.4, secondary threshold of p=0.05) overlaid onto a standard structural image. The red to yellow color scale displays regions in which CBF is higher for normal weight BD compared to overweight/obese BD.
| Table 1. Demographic Characteristics of Study Groups |
|-----------------------------------------------|
| **BD<sub>OW/OB</sub>** (n = 25) | **BD<sub>NW</sub>** (n = 55) | **HC** (n = 61) | **Test** | **p-value** | **Effect Size** |
| Age | 17.32 ±1.27 | 17.32 ±1.45 | 16.73 ±1.77 | F=2.40 | 0.09 | η²=0.03 |
| Sex (% female) | 16 (64) | 35 (64) | 32 (53) | χ²=1.82 | 0.40 | V=0.11 |
| SES | 4.16 ±1.03 | 4.27 ±0.85 | 4.33 ±0.96 | H=0.79 | 0.67 | η²=0.01 |
| Race (% Caucasian) | 14 (56)<sup>a</sup> | 46 (84)<sup>b</sup> | 36 (59)<sup>a</sup> | χ²=10.11 | 0.006 | V=0.27 |
| Intact family (%) | 15 (60) | 33 (60) | 38 (62) | χ²=0.08 | 0.96 | V=0.02 |
| Tanner stage (1-5) | 4.56 ±0.65 | 4.38 ±0.62 | 4.18 ±0.67 | H=6.89 | 0.03 | η²=0.04 |
| BMI (adjusted) | 29.1 ±3.94<sup>b</sup> | 21.6 ±1.99<sup>a</sup> | 20.6 ±1.87<sup>a</sup> | H=65.86 | <0.001 | η²=0.45 |
| BMI percentile<sup>a</sup> | 92.55 ±1.19<sup>b</sup> | 52.75 ±3.10<sup>a</sup> | 46.34 ±3.06<sup>a</sup> | H=56.73 | <0.001 | η²=0.40 |
| Waist circumference<sup>a</sup> | 89.89 ±7.93<sup>b</sup> | 74.36 ±6.47<sup>a</sup> | 72.66 ±6.07<sup>a</sup> | H=46.58 | <0.001 | η²=0.35 |
| CGAS – Most severe past | 43.84 ±9.05 | 43.48 ±8.72 | -- | U= 660 | 0.87 | d=0.04 |
| CGAS – Past month<sup>b</sup> | 66.80 | 68.87 | 88.34 | ±19.15<sup>b</sup> | ±11.99<sup>b</sup> | ±6.44<sup>a</sup> | F= 95.41 | <0.001 | η²=0.54 |
| CGAS – Current<sup>b</sup> | 62.52 | 64.94 | 88.36 | ±11.42<sup>b</sup> | ±12.49<sup>b</sup> | ±6.11<sup>a</sup> | F=118.16 | <0.001 | η²=0.60 |

**Note.** Values are reported in mean ± standard deviation unless otherwise specified. a,b=different superscripts denote a significant difference between different groups at p = 0.05. SES=socio-economic status; BMI=body mass index; CGAS=Children’s Global Assessment Scale. α=missing data points: BMI percentile-2 BD<sub>OW/OB</sub>, 4 BD<sub>NW</sub>, 5 HC; waist circumference-3 BD<sub>OW/OB</sub>, 6 BD<sub>NW</sub>, 3 HC. β = Homogeneity of variance violated, Welch test reported.
Table 2. Clinical Characteristics of BD_{NW} and BD_{OW/OB} Groups

|                          | BD_{NW}      | BD_{OW/OB}     | Test Statistic | p-value | Effect Size |
|--------------------------|--------------|----------------|----------------|---------|-------------|
| BD-I (%)                 | 22 (40)      | 8 (32)         | χ²=0.57        | 0.75    | V=0.09      |
| BD-II (%)                | 14 (25)      | 8 (32)         |                |         |             |
| BD-NOS (%)               | 19 (35)      | 9 (36)         |                |         |             |
| Age of onset             | 15.04 ± 2.54 | 14.65 ± 2.30   | U=592.50       | 0.32    | d=0.16      |

**Clinical Characteristics**

| Lifetime psychosis (%)  | BD_{NW}  | BD_{OW/OB} | Test Statistic | p-value | Effect Size |
|-------------------------|----------|------------|----------------|---------|-------------|
|                         | 6 (11)   | 4 (16)     | χ²=0.41        | 0.72    | V=0.07      |
| Lifetime suicide attempts (%) | 8 (15) | 5 (20) | χ²=0.38        | 0.53    | V=0.07      |
| Lifetime self-injurious behavior (%) | 26 (47) | 14 (56) | χ²=0.52        | 0.47    | V=0.08      |
| Lifetime suicidal ideation (%) | 35 (64) | 14 (56) | χ²=0.42        | 0.52    | V=0.07      |
| Police contact/arrest (%) | 15 (27) | 2 (8)    | χ²=3.82        | 0.051   | V=0.22      |
| Lifetime physical and/or sexual abuse (%) | 5 (9) | 0 (0) | χ²=2.42        | 0.32    | V=0.17      |
| Lifetime psychiatric hospitalization (%) | 28 (51) | 10 (40) | χ²=0.82        | 0.37    | V=0.10      |
| Current depression score | 14.58 ±10.91 | 18.28 ±12.45 | U=798.00       | 0.25    | d=0.32      |
| Lifetime depression score | 29.49 ±12.65 | 30.80 ±11.60 | U=704.00       | 0.86    | d=0.11      |
| Current mania score      | 9.35 ±10.30 | 10.12 ±10.57 | U=708.50       | 0.82    | d=0.07      |
| Lifetime mania score     | 30.71 ±9.89 | 32.52 ±12.22 | t=-0.70        | 0.48    | d=0.16      |

**Lifetime Comorbid Diagnoses**

| ADHD (%)                | BD_{NW} | BD_{OW/OB} | Test Statistic | p-value | Effect Size |
|-------------------------|---------|------------|----------------|---------|-------------|
|                         | 26 (47) | 10 (40)    | χ²=0.37        | 0.54    | V=0.07      |
| Disorder                  | Group 1 | Group 2 | $\chi^2$ | df | $p$-value | V | $\alpha$-value |
|---------------------------|---------|---------|----------|----|-----------|---|----------------|
| Any anxiety (%)           | 41 (75) | 21 (84) | 0.88     | 1  | 0.35      | 0.11 | 0.11 |
| ODD (%)                   | 9 (16)  | 11 (44) | 7.00     | 1  | 0.008     | 0.30 | 0.30 |
| CD (%)                    | 2 (4)   | 1 (4)   | 0.006    | 1  | > 0.99    | 0.01 | 0.01 |
| Nicotine use (yes/no) (%) | 7 (13)  | 4 (16)  | 0.16     | 1  | 0.73      | 0.04 | 0.04 |
| Any SUD                   | 12 (22) | 6 (24)  | 0.05     | 1  | > 0.99    | 0.02 | 0.02 |
| Anorexia nervosa (%)      | 1 (2)   | 1 (4)   | 0.34     | 1  | 0.53      | 0.65 | 0.65 |
| Bulimia nervosa (%)       | 3 (5)   | 2 (8)   | 0.19     | 1  | 0.65      | 0.05 | 0.05 |
| Eating disorder-NOS (%)   | 12 (22) | 6 (24)  | 0.05     | 1  | 0.83      | 0.02 | 0.02 |

**Family Psychiatric History**

| Disorder                  | Group 1 | Group 2 | $\chi^2$ | df | $p$-value | V | $\alpha$-value |
|---------------------------|---------|---------|----------|----|-----------|---|----------------|
| Mania/hypomania (%)       | 26 (47) | 12 (48) | 0.004    | 1  | 0.95      | 0.01 | 0.01 |
| Depression (%)            | 39 (71) | 18 (72) | 0.01     | 1  | 0.92      | 0.01 | 0.01 |
| Anxiety (%)               | 31 (56) | 17 (68) | 0.97     | 1  | 0.33      | 0.11 | 0.11 |
| ADHD (%)                  | 18 (33) | 6 (24)  | 0.62     | 1  | 0.43      | 0.09 | 0.09 |

**Lifetime Medications**

| Medication               | Group 1 | Group 2 | $\chi^2$ | df | $p$-value | V | $\alpha$-value |
|--------------------------|---------|---------|----------|----|-----------|---|----------------|
| SGA (%)                  | 42 (76) | 17 (68) | 0.62     | 1  | 0.43      | 0.09 | 0.09 |
| Lithium (%)              | 13 (24) | 7 (28)  | 0.18     | 1  | 0.68      | 0.05 | 0.05 |
| SSRI antidepressants (%) | 15 (27) | 10 (40) | 1.30     | 1  | 0.26      | 0.13 | 0.13 |
| Non-SSRI antidepressants (%) | 10 (18) | 6 (24)  | 0.36     | 1  | 0.55      | 0.07 | 0.07 |
| Stimulants (%)           | 12 (22) | 4 (16)  | 0.36     | 1  | 0.55      | 0.07 | 0.07 |

**Current Medications**

| Medication               | Group 1 | Group 2 | $\chi^2$ | df | $p$-value | V | $\alpha$-value |
|--------------------------|---------|---------|----------|----|-----------|---|----------------|
| SGA (%)                  | 35 (64) | 13 (52) | 0.97     | 1  | 0.33      | 0.11 | 0.11 |
| Lithium (%)              | 8 (15)  | 7 (28)  | 2.04     | 1  | 0.22      | 0.16 | 0.16 |
| SSRI antidepressants (%) | 3 (5)   | 4 (16)  | 2.39     | 1  | 0.20      | 0.17 | 0.17 |
| Non-SSRI antidepressants (%) | 2 (4)   | 2 (8)   | 0.69     | 1  | 0.59      | 0.09 | 0.09 |
| Stimulants (%)           | 5 (9)   | 0 (0)   | 2.42     | 1  | 0.32      | 0.17 | 0.17 |

**Note.** Values are reported in mean ± standard deviation unless otherwise indicated. $\alpha$=p-value
reported from Fisher’s Exact Test. NOS=Not Otherwise Specified; Depression Score Based on Depression Rating Scale; Mania Score Based on Mania Rating Scale; ADHD=Attention Deficit-Hyperactivity Disorder; SUD=Substance Use Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder; SGA=Second Generation Antipsychotic; SSRI=Selective Serotonin Reuptake Inhibitor.
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 $\eta^2$ | $P$    |
| Global   |                  |                |            |            |                |        |
| Gray     | 63.63 (9.84)     | 66.75 (13.21)  | 63.58 (11.43) | 1.18       | 0.02            | 0.31   |
| Matter   |                  |                |            |            |                |        |
| ACC      | 72.82 (9.93)     | 76.14 (16.77)  | 72.25 (14.89) | 1.06       | 0.02            | 0.35   |
| Amygdala | 42.58 (8.59)     | 43.86 (10.71)  | 41.21 (11.14) | 0.91       | 0.01            | 0.41   |

$CBF$ values are reported in $\text{mL/100 g/min}$ (mean ± standard deviation); ACC and amygdala $CBF$ values were extracted from masks restricted to GM voxels. Unadjusted $p$-values are reported.
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                  |
Figure 2
Figure 3