Mood-related Differences in Cerebral Blood Flow in Adolescents with Bipolar Disorder

Simina Toma

A thesis submitted in conformity with the requirements for the degree of

Master of Science

Graduate Department of Pharmacology and Toxicology

University of Toronto

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Year of Convocation – 2019

Abstract (146/150)

Numerous adult bipolar disorder (BD) studies have examined cerebral blood flow (CBF) in relation to mood, whereas little is known on this topic in adolescents. We enrolled 129 adolescents (mean age 17.34+/-1.42 years), including 72 BD (28 hypomanic/mixed, 19 depressed, 25 euthymic) and 57 healthy controls (HC). Pseudocontinuous arterial spin labeling (ASL) magnetic resonance imaging (MRI) evaluated CBF, using both a region of interest and whole brain voxel-wise approach. Within-BD analysis examined the association of mania and depression severity with CBF. We found differences in terms of CBF between groups with higher CBF in the BD euthymic group than in HC and symptomatic BD in temporal, precentral, and occipital regions. Severity of depressive symptoms in BD was negatively correlated with CBF in the anterior cingulate cortex and temporal regions. Higher CBF in euthymic BD adolescents may reflect developmentally-specific compensatory CBF regulation mechanisms required to maintain euthymia.

Acknowledgments

This project could never have been possible without the assistance and support of the entire team at the Center for Youth Bipolar Disorder (CYBD) as well as the study participants and their families.

First, I wish to thank my supervisor, Dr. Benjamin Goldstein, for his excellent mentorship throughout my graduate degree and beyond. I have only started research in mid-residency, and Dr. Goldstein has been an instrumental part of this through his commitment to academic excellence, intellectual generosity and constant support. He has certainly helped me grow as a researcher, as a clinician and as a person.

I also want to thank Anahit Grigorian for her outstanding work with imaging analysis and her support throughout this project and many others. Lisa Fiksenbaum has provided outstanding support and guidance for the statistical part of this project, and has greatly enhanced my knowledge of statistics. Vanessa Timmins, Danielle Omrin and Jessica Roane have provided tremendous support through their commitment to all aspects of CYBD and have always done so with kindness and care. Alysha Sultan, my fellow graduate student in pharmacology has been a source of support as we have navigated the program side by side.

Dr. Bradley MacIntosh and his lab, especially Nicholas Luciw, have greatly assisted with the genesis and progression of this project, through their creative thinking and outstanding collaboration. I also want to thank Dr. Walter Swardfager, my advisor, for his valuable input and teaching.

Finally, I want to acknowledge my colleagues and friends in the Clinician Scientist Program in the Department of Psychiatry at the University of Toronto who have always

been there to support the integration of clinical work and research, through the wonders and challenges of residency and fellowship.

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ACC- Anterior Cingulate Cortex, ADHD- Attention Deficit Hyperactivity Disorder, ASL- Arterial Spin Labelling, BD- Bipolar Disorder, BD-I- Bipolar I Disorder; BD-II- Bipolar II Disorder; BD-NOS- Bipolar Disorder Not Otherwise Specified, BDNF- Brain-Derived Neurotrophic Factor, BMI- Body Mass Index, CBF- Cerebral Blood Flow, CD- Conduct Disorder, CGAS- Children's Global Assessment Scale, CVD- Cardiovascular Disease, DLPFC- Dorsolateral Prefrontal Cortex, DRS- Depression Rating Scale, FSL- FMRIB Software Library, GLM- General Linear Model, GM- Grey Matter, HC- Healthy Control, K-SADS-PL- Kiddie-Schedule for Affective Disorders and Schizophrenia- Present and Lifetime Version, MDD- Major Depressive Disorder, MRI- Magnetic Resonance Imaging, MRS- Mania Rating Scale, NO- Nitric Oxide, OFC- Orbitofrontal Cortex, PET- Positron Emission Tomography, ROI- Region of Interest, SD- Standard Deviation, SES- Socio Economic Status, SGA- Second-Generation Antipsychotic, SPECT- Single-Photon Emission Computerized Tomography, SSRI- Selective Serotonin Reuptake Inhibitor, SUD- Substance Use Disorder, VLPFC- Ventrolateral Prefrontal Cortex, VMPFC- Ventromedial Prefrontal Cortex, WC- Waist Circumference.

1. Introduction

1.1 Statement of problem

Bipolar disorder (BD) is a chronic episodic mood disorder characterised by the alternation of periods of mania or hypomania and depression, as well as periods of normal mood, called euthymia(American Psychiatric Association, 2013). BD is associated with significant functional impairment and is among the leading causes of disability worldwide(Whiteford et al., 2013)(Judd et al., 2005)(Simon et al., 2007). Onset of BD prior to adulthood is common, and studies have found increased symptomatic burden and disease severity in both clinical and epidemiological samples with earlier onset(Perlis et al., 2009)(Post et al., 2010)(Goldstein and Levitt, 2006). The prevalence of BD in large studies has been found to be around 2-5 %, both in adults and adolescents(Judd and Akiskal, 2003)(Kessler et al., 2005)(Lewinsohn et al., 1995)(Merikangas et al., 2009)(Merikangas et al., 2010).
The longitudinal course of BD is characterized by a greater time spent in depression than mania or hypomania, both in adults and adolescents(Judd et al., 2003)(Birmaher et al., 2009)(Kupka et al., 2007). BD depression is associated with suicidality, and treatment resistance is common(Frye et al., 2014)(Valtonen et al., 2008)(Hawton et al., 2005)(Post et al., 2003). Furthermore, although cognitive deficits in BD persist during euthymia, several studies found worst cognitive performance during depressive episodes(Kurtz and Gerraty, 2009)(Malhi et al., 2007). In addition, several studies have found that BD is associated with cardiovascular disease earlier than in the general population (Goldstein, 2017; Goldstein et al., 2015a; Swartz and Fagiolini, 2012).

The diagnosis of BD remains clinical and overall there have been few new treatments or treatment targets in the past few years. The present treatments for BD depression, which represents the main burden of BD and longitudinal course(Judd et al., 2003), are suboptimal and there is frequent treatment resistance(Bauer et al., 2018). New treatments for BD require the understanding of the biological underpinning of mood states in BD. Neuroimaging can assist in investigating both the state and trait abnormalities of brain functioning in BD. As BD has a frequent onset during adolescence and early adulthood, investigation in those populations may assist with understanding the early stages of illness and contributory factors without the confounding effects of long illness duration or longstanding medication impact. Questions arise as to the putative involvement of vascular factors in BD pathophysiology at the neurofunctional level given the known relationship between BD and cardiovascular disease, and as to the best method of assessing vascular function in BD and linking neurovascular changes and BD disease course. Although the exact pathophysiology of BD is unknown, recent models of BD, informed by structural and functional imaging studies, evoke disruptions in prefrontal-subcortical circuits (Strakowski et al., 2012). Measure of cerebral blood flow (CBF) may be a useful additional functional neuroimaging measure in BD, directly capturing perfusion (synonymous with CBF) at a regional level, with opportunities for quantification. A recent review has identified reproduced abnormalities in terms of CBF in adults with BD, particularly during mood episodes, although sample sizes for each study are small and little is known about CBF in youth with BD.

1.2 Review of literature

1.2.1 Bipolar disorder in adolescents

BD is a severe episodic mood disorder characterised by episodes of mania, hypomania and depression as well as periods of euthymia, or normal mood(American Psychiatric Association, 2013). A major depressive episode is defined as a period of over two weeks of persistent low mood, anhedonia or loss of pleasure in activities previously enjoyed with associated symptoms such as negative thoughts, changes in terms of energy level, appetite and sleep as well as possible suicidal ideation or psychosis. Periods of mania or hypomania are defined as episodes of over four (or days days) of elated mood, decreased need for sleep, increased energy, increased activity and productivity, increased speech and thought rate and impulsivity with possible involvement in activities with high risk for negative consequences. Onset of BD is frequently during adolescence and young adulthood and up to half of patients with BD experience their first mood episode in childhood or adolescence(Perlis et al., 2004). Early onset is associated with greater overall symptom severity and recurrence, higher rates of comorbidity, more hospitalization and more suicide attempts(Post et al., 2010)(Goldstein and Levitt, 2006) (Perlis et al., 2009). In a longitudinal study, adolescents with BD were found to be asymptomatic for 41% of weeks, to have major depressive episodes for 6% of the follow up time, and hypomania or mania 2.7% of time(Birmaher et al., 2009). Youth were found to have subsyndromal mood symptoms for 42% of the follow up time(Birmaher et al., 2009).

1.2.2 Bipolar disorder and cardiovascular burden

There is a known link between BD and cardiovascular disease (CVD) risk, with excessive and premature morbidity and mortality (Goldstein, 2017; Goldstein et al., 2015a; Swartz and Fagiolini, 2012). CVD and its complications are the leading cause of mortality in BD, and the most common medical conditions in BD (Kilbourne et al., 2004; Westman et

al., 2013). In comparison to healthy controls (HC) individuals with BD have an adjusted CVD mortality rate ratio of 1.5-2.5 and CVD mortality 10 years earlier than in the general population (Weeke et al., 1987; Westman et al., 2013). In addition, the age of onset of new CVD was found to be up to 17 years premature in BD (Goldstein et al., 2015b). Metabolic syndrome and its components of obesity, hypertension, high cholesterol levels and type II diabetes are also elevated in those with BD (Cardenas et al., 2008; Fiedorowicz, 2008; Johannessen et al., 2006). This association between CVD and BD is in excess of what can be explained by psychotropic medication, lifestyle behaviors and even traditional CVD risk factors (Benjamin I. Goldstein et al., 2009; Goldstein et al., 2015a, 2015b; Kraepelin, 1921; Tsuang et al., 1980). Furthermore, the association between BD and CVD is thought to be impacted by longitudinal mood symptomatic burden (Fiedorowicz et al., 2009)(Fiedorowicz et al., 2014)(Fiedorowicz et al., 2012). Specifically, one prospective study found that the burden of mania or hypomania predicted cardiovascular mortality (Fiedorowicz et al., 2009) and another study found that duration of severe depressive episode was predictive of vascular mortality(Fiedorowicz et al., 2012).

1.2.3 Neuroimaging models of bipolar disorder

Contemporary neuroimaging models of BD describe functional and structural differences in circuits implicated in emotion processing and emotional regulation, as well as abnormalities in neural circuitry related to reward processing (Phillips and Swartz, 2014). Anomalous connectivity between ventral prefrontal networks and limbic structures, especially the amygdala, is hypothesized to be at the center of a disruption causing structural and functional reorganization, and BD symptom emergence(Strakowski et al., 2012). Strakowski and colleagues describe two main prefrontal networks connected with

the amygdala and ventral striatum: (1) a ventromedial loop involved in internally referenced emotions which includes the ventromedial prefrontal cortex/orbitofrontal cortex (VMPFC/OFC) and subgenual anterior cingulate cortex (sgCC), as well as (2) a ventrolateral circuit implicated in the appraisal of external emotional stimuli which involves the ventrolateral prefrontal cortex (VLPFC) and rostral anterior cingulate cortex (ACC)(Strakowski et al., 2012). Recently, replicated findings have emerged regarding reduced cortical thickness in adults with BD, particularly in the left anterior cingulate, paracingulate, left superior temporal regions, dorsolateral prefrontal cortex (DLPFC), VLPFC and OFC(Hanford et al., 2016). Although amygdala volume reduction has been consistently replicated in youth with BD(Pfeifer et al., 2008)(DelBello et al., 2004)(Hilary P Blumberg et al., 2003)(Kelley et al., 2013), neurostructural findings regarding prefrontal and temporal cortical abnormalities have been less consistent(Jean A. Frazier et al., 2005)(Wilke et al., 2004)(Dickstein et al., 2005)(Hajek et al., 2008)(Kaur et al., 2005).

1.2.4 Cerebral blood flow

CBF is commonly defined as the volume of blood delivered to the brain tissue per minute, and is a core metric of brain health(Peterson et al., 2011)(Fantini et al., 2016). As the brain has high energy demands alongside limited energy reserves, cerebrovascular circulation must supply the metabolically active regions with glucose and oxygen, adapt to changes in systemic blood pressure, and ensure homeostasis via brain temperature regulation and disposal of toxic metabolites(Iadecola, 2017; Paulson et al., 2009). CBF is proportional to brain activity, and there is normally a coupling between metabolically active regions and CBF(Hoge et al., 1999; Leenders et al., 1990). There are two main hypotheses regarding the coupling of CBF with brain activation: a “feedback” hypothesis stipulating

that hypoxia would engender increased blood flow via carbon dioxide (CO_2), lactate and adenosine and a "feed forward" hypothesis in which the increased blood flow would be triggered by synaptic activity via release of nitric oxide (NO) or prostanoids(Iadecola, 2017). However, in abnormal disease states such as hypertension, cerebral microvascular disease, or Alzheimer's disease, a decoupling is observed(Girouard, 2006; Østergaard et al., 2013). Neurovascular decoupling can reduce the necessary functional hyperemia which would lead to hypoxia and possibly ischemic damage(Girouard, 2006). Lower CBF is also associated with a higher cardiometabolic risk profile, and with white matter hyperintensities, possibly predating the onset of these lesions(Brickman et al., 2009; Jennings et al., 2013; Shi et al., 2016). Both absolute CBF and CBF regulation in response to stimuli have been found to decrease with age and vascular pathology especially in regions associated with neurocognitive impairment(Leoni et al., 2017; Shaw et al., 1984). CBF abnormalities have been previously described in patients with Major Depressive Disorder (MDD) and Schizophrenia(Liddle et al., 1992; Liu et al., 2016; Videbech, 2000).

CBF can be measured using different methods. Single-photon emission computerized tomography (SPECT) is a functional nuclear tomographic imaging technique in which a gamma-ray emitting radiotracer is injected, allowing for an assessment of three-dimensional distribution of the radiotracer, reflecting CBF(Juni et al., 2009). SPECT is more widely available and less costly than other methods, but only provides relative, not absolute, measure of CBF with spatial resolution limitations(Wintermark et al., 2005). Positron emission tomography (PET) is a functional nuclear imaging technique detecting gamma-rays using substances of interest labeled with positron emitting radioisotopes, followed by a scan and an anatomical correlation with CT or MRI(Raichle et al., 1983).

PET allows for quantitative measurement of CBF and repeated measures, and allows for the study of multiple parameters including glucose uptake by using different substances of interest labelled with radiotracers (Wintermark et al., 2005). Furthermore, ^{15}O-water PET is considered the gold standard for quantitative measurement of CBF(Herscovitch et al., 1983). However, both PET and SPECT are associated with exposure to radiation and require availability of radiotracers(Wintermark et al., 2005). The exposure to radiation renders these techniques restricts the use of these techniques in children and adolescents. Finally, dynamic susceptibility contrast from an intravenous contrast agent and arterial spin labeling (ASL) are examples of MRI methods. ASL has the advantage of being a completely non-invasive MRI method using magnetically labeled water as an endogenous tracer to measure absolute CBF(Borogovac and Asllani, 2012; Detre et al., 2009; Liu and Brown, 2007). ASL is quantitative, amenable to intra- or inter-session repeated acquisitions and is available on clinical MRI scanners. There is good concordance between ^{15} O-water PET and ASL measures of CBF(Zhang et al., 2014). Disadvantages include the requirement for a high signal to noise ratio, possible inaccuracy of measurement in context of particularly high or low CBF, and contraindications to MRI (Wintermark et al., 2005).

1.4.5 A review of cerebral blood flow in bipolar disorder

A review of the literature on CBF in BD identified a total of 33 studies with 508 participants with BD, and 538 controls. Studies are presented below and in Tables 1 and 2.

Cerebral blood flow in bipolar disorder in comparison to healthy controls at rest

19 studies compared BD to HC subjects at rest, of which ten compared subjects with BD depression to HC (see Table 1).

Bipolar depression in comparison to healthy controls: Six studies totaling 88 BD subjects and 155 HC found reduced CBF in the BD-depression group in comparison to HC. Regions include the anterior temporal cortex and left parietal cortex(Bhardwaj et al., 2010), left superior temporal, right parietal and bilateral occipital(Bonne et al., 1996), bilateral anterior superior and middle frontal gyri, right anterior cingulate cortex (ACC), left anterior superior temporal gyrus, left angular gyrus, left lingual gyrus and bilateral anterior insular cortex(Ito et al., 1996), left dentate nuclei of the cerebellum(Zhao et al., 2016) and the subgenual prefrontal cortex(Drevets et al., 1997). One study found a lower global CBF in BD vs HC(Dunn et al., 2005). Conversely, one study reported increased resting CBF in 22 BD-depression subjects in comparison to 19 HC in the left precentral gyrus, left precuneus, left inferior parietal lobe, left posterior cingulate, right lingual gyrus and right middle temporal gyrus(Cantisani et al., 2016). Four studies did not find differences between a total of 61 BD subjects in depression and 75 HC(Cantisani et al., 2016; Ebert et al., 1993; Tutus et al., 1998; Zhao et al., 2017). However one study among these found a lower CBF ratio of the left to right hemispheres in BD subjects than in HC(Delvenne et al., 1990).

Bipolar mania in comparison to healthy controls: Three studies totaling 26 subjects with mania and 38 HC found decreased CBF in BD subjects in the left frontal, left parietal and left ACC(Bhardwaj et al., 2010), in the right temporal lobe(Migliorelli et al., 1993), and in anterior cortical regions, as well as a reduction of the normal anterioposterior gradient in BD subjects(Rubin et al., 1995). Increased severity of psychotic symptoms was associated with reduced CBF in subjects with mania(Bhardwaj et al., 2010).One study did not find differences in CBF between 30 subjects with BD-mania and 30 HC(Silfverskiöld and Risberg, 1989).

Bipolar euthymia in comparison to healthy controls: One study found lower CBF in multiple regions including temporal, occipital, medial frontal and cingulate regions in euthymic adults with BD (n=16) in comparison to controls (n=10), especially in the cingulate gyrus(Culha et al., 2008). Another study did not find differences between 8 euthymic BD subjects and 20 HC(Uytdenhoef et al., 1983).

Bipolar disorder in various mood states in comparison to healthy controls: One study found increased left frontal and temporal cerebral blood volume in 14 BD subjects in various mood states in comparison to 29 HC. Furthermore, whereas in normal subjects left frontal CBF was greater than right side CBF, the opposite was found in BD subjects(Agarwal et al., 2008). A second study found lower cerebellar blood volume in a group of 10 BD subjects in various mood states, in comparison to 10 HC(Loeber et al., 1999). A third study did not find differences in terms of CBF between 21 BD subjects in various mood states and 21 HC(Varga et al., 2009). The only study in adolescent BD subjects (n=31) in various mood states vs 20 HC found increased CBF in medial frontal and middle cingulate regions in adolescents with BD compared to controls(MacIntosh et al., 2017).

Cerebral blood flow in relation to cognitive and emotional tasks

Table 2 presents the results of 14 studies examining CBF in BD during various cognitive and emotional tasks, or in relation to specific variables such as treatment discontinuation or exercise.

Cognitive tasks: One study used a memory task to compare 22 BD subjects in various mood states with 24 HC and found lower CBF in BD relative to HC(Wood and Flowers, 1990). A second study examining a reaction time task, comparing 13 euthymic BD subjects with 14

HC, found that the task elicited increased CBF in different areas: prefrontal and limbic in BD, parietal and premotor in HC(Berns et al., 2002). A third verbal learning task study comparing eight euthymic BD subjects with eight HC found blunted task-related CBF response in BD in the dorsolateral prefrontal cortex (DLPFC)(Deckersbach et al., 2006). In a Stroop-type task, no difference in terms of CBF was found between 28 euthymic BD subjects and 36 HC. A study comparing six euthymic BD subjects with 10 HC and 10 subjects with schizophrenia in a verbal fluency task paradigm did not find differences between groups(Dye et al., 1999). A gambling-type task study of six BD-mania subjects, six MDD subjects and 10 HC, found task-related increased CBF in the mania group in dorsal ACC, and task related decreased CBF in left frontal pole in mania(Rubinsztein et al., 2001). A study of 30 BD subjects found a correlation between low resting frontal CBF. Another study of 27 BD subjects found increased CBF in the left inferior frontal gyrus after a four-week cognitive training program(Venza et al., 2016). Four of the aforementioned studies report on correlations between CBF and cognitive performance, noting that lower CBF was associated with poorer performance on measured tasks of memory(Wood and Flowers, 1990)(Benabarre et al., 2005), verbal learning (Benabarre et al., 2005), response inhibition(Dev et al., 2015), and complex abstraction(Venza et al., 2016). In contrast, poor psychomotor performance was related to higher anterior temporal CBF and worse performance in a Stroop-type task was associated with higher CBF in striatal and temporal regions(Benabarre et al., 2005).

Emotional tasks: A study comparing 11 depressed BD subjects with nine euthymic BD subjects found differential CBF changes in the context of a sad-mood provocation task. Euthymic subjects had a unique increase in CBF in dorsal ACC and premotor cortex and

decrease in CBF in the orbitofrontal cortex. Depressed subjects had a decrease in CBF in lateral prefrontal regions with sad mood provocation. There was a greater magnitude of decrease in CBF in dorsal ventral medial frontal regions between baseline and mood induction in euthymic group vs depressed group(Krüger et al., 2003). Another study using this induced transient sadness paradigm in nine euthymic BD subjects who were found to be lithium responsive, nine euthymic BD valproate responders and nine healthy siblings. This study found a unique decreased CBF in medial frontal cortex with mood induction in the BD groups, while an increase in CBF was found in healthy siblings(Krüger et al., 2006).

CBF in relation to other variables

A study looking at 14 BD subjects pre- and post-eight weeks of lithium discontinuation found increased CBF in the posterior region of the left mid/inferior temporal cortex as well as decreased CBF in the left ACC (Goodwin et al., 1997). A study performing serial scans in 12 BD subjects in various mood states found an asymmetric CBF pattern (right greater than left) in anterior parts of the temporal lobe in BD subjects in depression and mania, but not during euthymia(Gyulai et al., 1997). In the only study looking at the impact of exercise on CBF, elevated CBF in medial frontal and middle cingulate regions in 31 adolescents with BD compared to 20 healthy controls was temporarily abolished after a bout of aerobic exercise(MacIntosh et al., 2017).

Cerebral blood flow in bipolar disorder in comparison to major depressive disorder

Eight studies with a total of 113 subjects with MDD and 107 BD subjects in a depressive episode, did not find significant differences between CBF patterns in MDD and in BD depression(Bonne et al., 1996; Delvenne et al., 1990; Drevets, 1997; Dunn et al., 2005; Ito et al., 1996; Wood and Flowers, 1990; Zhao et al., 2017, 2016). In contrast, a

CBF study using pattern recognition analysis of ACC among women (n=18 BD depression, n=18 MDD depression, n=18 controls) differentiated BD depression from unipolar depression with 81% accuracy(Almeida et al., 2013). Comparing 10 subjects with MDD with 20 BD in various mood states, and 10 HC, this study found different areas of lower CBF in BD and MDD in comparison to HC, mainly in left fronto-temporal regions in BD and in bilateral anterior temporal and frontal regions in MDD(Bhardwaj et al., 2010). While an increase in CBF was found in 22 BD subjects currently depressed in left prefrontal regions, this was not found in 20 subjects with MDD and 19 HC(Cantisani et al., 2016). CBF differences between six subjects with mania and 10 HC in a decision making task were not found between MDD and HC(Rubinsztein et al., 2001). Two studies totaling 15 BD in various mood states, 26 sujects with MDD and 29 HC found left frontal increased CBF in MDD in comparison to the other groups(Tutus et al., 1998; Uytdenhoef et al., 1983).

In summary, the most consistent finding in the current literature on CBF in BD is reduced CBF in adults with BD depression, mostly in frontal, temporal and parietal regions. There are also findings of abnormal CBF response to cognitive or emotional tasks, mainly of decreased reactivity in contrast to HC. Studies also report on correlation between higher CBF in frontal and parietal regions and greater cognitive performance. There are limited CBF differences between BD depression and MDD. Of note, there have also been contradictory findings in terms of CBF in BD in contrast to HC. Few studies found an increase in CBF in frontal and temporal regions in BD depression or in a group of BD subjects in different mood states in contrast to HC. Only one study had previously examined CBF in BD adolescents, and found elevated CBF in BD in frontal and cingulate

regions. Overall these findings suggest that CBF is affected in BD adults, and specifically in regards to mood episodes and particularly depression. Limitations in terms of the available literature on CBF in BD include small sample size for each study, use of different imaging methods and various paradigms for studies examining the CBF response to stimuli. This limits comparisons between studies. Importantly, there is also a scarcity of studies in youth, in participants at different stages of illness, and that examine CBF repeatedly over time and/or across different mood states .

Table 1. Review of cerebral blood flow studies in bipolar disorder at rest

Bipolar depression n=131 BD n=207 HC	↓ Anterior temporal cortex and left parietal cortex (n=10 BD; n=20 HC)(Bhardwaj et al., 2010)
	↓ Left superior temporal, right parietal and bilateral occipital (n=9 BD; n=21 HC)(Bonne et al., 1996)
	↓ Bilateral anterior superior and middle frontal gyri, right ACC, left anterior superior temporal gyrus, left angular gyrus, left lingual gyrus and bilateral anterior insular cortex (n=6 BD; n=9 HC)(Ito et al., 1996)
	↓ Left dentate nuclei of the cerebellum (n=35 BD; n=45 HC)(Zhao et al., 2016)
	↓ Subgenual prefrontal cortex (n=19 BD; n=51 HC)(Drevets et al., 1997)
	↓ Global (n=9 BD; n=9 HC)(Dunn et al., 2005)
	↔ and relative left to right decreased CBF (n=8 BD; n=16 HC)(Delvenne et al., 1990)
	↑ Left precentral gyrus, left precuneus, left inferior parietal lobe, left posterior cingulate, right lingual gyrus and right middle temporal gyrus (n=22 BD; n=19 HC)(Cantisani et al., 2016)
	↔ (n=6 BD; n=8 HC)(Ebert et al., 1993)
	↔ (n=7 BD; n=9 HC)(Tutus et al., 1998)
	↔ (n=45 BD; n=40 HC)(Zhao et al., 2017)
Mania n=46 BD n=68 HC	↓ Left frontal, left parietal and left ACC (n=10 BD; n=20 HC)(Bhardwaj et al., 2010)
	↓ Right temporal (n=5 BD; n=7 HC)(Migliorelli et al., 1993)
	↓ Anterior cortical regions, and reduction of the normal anteroposterior gradient in BD subjects (n=11 BD; n=11 HC)(Rubin et al., 1995)
	↔ (n=30 BD; n=30 HC)(Silfverskiöld and Risberg, 1989)
Euthymia n=24 BD	↓ Widespread, especially in the cingulate gyrus (n=16 BD; n=10 HC)(Culha et al., 2008)

n=30 HC	↔ (n=8 BD; n=20 HC)(Uytdenhoef et al., 1983)
Various mood states n=76 BD n=80 HC	↓ Cerebellar blood volume (n=10 BD; n=10 HC)(Loeber et al., 1999)
	↑ Left frontal and temporal, inverse laterality index in frontal cortex (n=14 BD; n=29 HC)(Agarwal et al., 2008)
	↑ Medial frontal and middle cingulate (adolescents) (n=31 BD; n=20 HC)(MacIntosh et al., 2017)
	↔ (n=21 BD; n=21 HC)(Varga et al., 2009)

Table 2. Review of cerebral blood flow studies in bipolar disorder during tasks

Cognitive Tasks n=140 BD n=102 HC	•**Memory task:** ↓ (n=22 BD; n=24 HC)(Wood and Flowers, 1990) •**Serial reaction time task**: different regions of increased CBF: prefrontal and limbic in BD; parietal and pre-motor in HC (n=13 BD; n=14 HC)(Berns et al., 2002) •**Verbal learning task**: ↓ DLPFC (n=8 BD; n=8 HC)(Deckersbach et al., 2006) •**Color-word inhibition task**: ↔ and better performance in BD if higher resting CBF in ACC, inferior parietal lobule and DLPFC (n=28 BD; n=36 HC)(Dev et al., 2015) •**Verbal fluency task**: ↔ (n=6 BD; n=10 HC)(Dye et al., 1999) •**Decision making task**: ↑ dorsal ACC and ↓ left frontal pole (n=6 BD-mania; n=10 HC)(Rubinsztein et al., 2001) •**Baseline CBF and subsequent cognitive performance** correlation between poorer performance on memory and verbal learning and low frontal CBF, poor psychomotor performance related to greater anterior temporal CBF (n=30 BD; no HC)(Benabarre et al., 2005) •**Before and after 4-week cognitive training**: increased CBF in left inferior opercular frontal gyrus (n=27 BD; no HC)(Venza et al., 2016)
Emotional Tasks n=38 BD n=9 HC	**Sad mood provocation:** •Decreased CBF medial frontal cortex (n=18 BD; n=9 HC)(Krüger et al., 2006) •Differential response in function of mood state in BD: Euthymic (n=9) increased dorsal ACC and premotor cortex, decreased CBF in OFC. Depressed (n=11) decreased CBF in lateral prefrontal regions(Krüger et al., 2003)
Other	•**Post lithium discontinuation:** increased CBF posterior region of the left mid/inferior temporal cortex, decreased CBF left ACC (n=14 BD; no HC)(Goodwin et al., 1997) •**Serial scans (longitudinal)** asymmetric pattern in anterior parts of the temporal lobe in BD depression and mania, but not during euthymia (n=12 BD; no HC)(Gyulai et al., 1997) •**Pattern recognition ACC blood flow**: differentiated unipolar vs bipolar depression with 81% accuracy (n=18 BD; n=18 MDD; n=18 HC)(Almeida et al., 2013)

	• **Exercise**: ↑ CBF in medial frontal and middle cingulate regions in adolescents with BD vs HC temporarily abolished after a bout of aerobic exercise (n=31 BD; n=20 HC)(MacIntosh et al., 2017)

1.3 Purpose of study and objectives

The purpose of this study was to examine differences in CBF across mood states in a relatively large sample of BD adolescents and HC. We compared CBF in euthymic, hypomanic/mixed and depressed BD subjects and HC at rest, using arterial spin labelling (ASL) magnetic resonance imaging (MRI). In the primary analysis, we examined CBF across the four groups in *a priori* regions of interest (ROI) based on previous literature on CBF and BD and on the neurofunctional model of BD(Strakowski et al., 2012): anterior cingulate cortex (ACC), middle frontal gyrus and amygdala. We have also included a mean measure of global gray matter (GM) CBF. We also performed a whole-brain vertex wise analysis. In addition, we examined the link between mania and depression severity scores and CBF in BD, both using an ROI and whole brain approach.

The objectives and hypotheses of this study were as follows:

Objective 1. Identify regional differences in CBF between HC adolescents and BD adolescents presently depressed, hypomanic/mixed and euthymic in *a priori* regions of interest (ROI) and in whole brain vertex-wise analyses.

H1. There will be group differences in CBF in the ACC, MFG and amygdala. *Post hoc* contrasts will demonstrate that CBF is lower in the BD depressed group than in the BD hypomanic/mixed, BD euthymic, and HC groups.

Objective 2. Identify brain regions of correlation between CBF and mania and depression scores using a region of interest and whole brain approach.

H2.1 Controlling for age and sex, lower CBF in the ACC and frontal regions will be associated with higher depression scores in the BD participants.

H2.2 Controlling for age and sex, higher mania scores will be associated with increased CBF in the amygdala.

Given limited prior studies on this topic, an exploratory whole brain analysis was also performed to complement the ROI approach. Other regions may be found to differ between the groups.

Our hypothesis of lower CBF in the BD depressed group is based on adult CBF studies which have identified lower CBF in BD participants during mania or depression in comparison to HC in frontal and temporal regions, although some studies did not find such differences(Bhardwaj et al., 2010; Bonne et al., 1996; Drevets et al., 1997; Ebert et al., 1993; Ito et al., 1996; Migliorelli et al., 1993; Silfverskiöld and Risberg, 1989; Tutus et al., 1998). However, it is thought that there may be differences between adolescents and adults based on prior studies of CBF and development in healthy populations(Satterthwaite et al., 2014), which may impact our findings and their comparison with adult findings. In contrast, only one study has examined CBF in BD adolescents using a subsample of the current sample, and found increased CBF in medial frontal and middle cingulate regions in 31 adolescents with BD compared to 20 HC; and no significant associations between CBF and

mood symptom, the study was not powered to evaluate for such associations(MacIntosh et al., 2017).

2 Materials and methods

2.1 Study design

This study assessed CBF in BD subjects across mood states and in HC using a cross-sectional design for practical purposes. All participants, as well as one parent or guardian, provided written informed consent prior to study participation. The study was approved by the Research Ethics Board at Sunnybrook Health Sciences Center and in accordance with the ethical principles of research as per the Declaration of Helsinski.

2.2 Participant selection

2.2.1 Participant recruitment

We recruited English-speaking adolescents between the ages of 13-20 years from the greater Toronto area. BD participants were recruited through the Center for Youth Bipolar Disorder, a subspecialized clinic and research center at Sunnybrook Health Sciences Center in Toronto. In addition, HC were recruited from the community through advertising in placed in the hospital, in public transit and in local community centers. Interested HC participants underwent a phone screening with a research assistant, followed by in-person visits.

2.2.2 Inclusion and exclusion criteria

Participants were included if they were English-speaking and from ages 13-20 years old. BD participants were included if they met the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) criteria for BD-I or BD-II(American Psychiatric

Association, 1994), or for BD-NOS. BD-NOS was defined using criteria previously operationalized by the Course and Outcome of Bipolar Illness in Youth (COBY) study group(Axelson et al., 2006): Elevated and/or irritable mood, plus 1) two *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV)(American Psychiatric Association, 1994) manic symptoms (three if only irritable mood is reported), 2) change in functioning, 3) mood and symptom duration of at least 4 hours during a 24 hour period, and 4) at least four cumulative 24 hour periods of episodes over the participants' lifetime that meet the mood, symptom severity, and functional change criteria.

To be included as HCs, participants must have had no lifetime mood or psychotic disorders, no alcohol or drug dependence or anxiety disorders within 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 condition, autoimmune disorder, inflammatory disorder, neurological or cognitive impairment or inability to provide consent.

2.3 Clinical and demographic characteristics

2.2.1 Interview instruments employed

Psychiatric diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version (K-SADS-PL)(Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, 1997), with expanded mood sections, the 13-item KSADS Depression Rating Scale (DRS)(Chambers et al., 1985) and the 13-item KSADS Mania Rating Scale (MRS)(Axelson et al., 2003), in place of the standard mood sections of the KSADS-PL. For DRS and MRS, information was obtained for the worst week in the past month (present) and the most severe past episode. The KSADS-PL is a semi-structured interview tool completed with the participant and a parent

or guardian aimed to assess present and past psychiatric diagnoses in children and adolescents age 8-18. Its reliability and validity have previously been studied(Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, 1997). Family history was determined using the Family History Screen interview (Weissman, 2000), and global functioning using the Children's Global Assessment Scale (CGAS)(Shaffer *et al.* 1983). The 4-factor Hollingshead Scale was used to ascertain socioeconomic status (SES)(Hollingshead, 1975). Current and past exposure to antidepressants, lithium and mood stabilizers, antipsychotics and stimulants was gathered using the Psychotropic Treatment Record from the Adolescent Longitudinal Interval Follow-Up Evaluation (ALIFE)(Keller et al., 1987).

Participants and their parents were interviewed and a consensus score was established. The interviewers involved in this study had completed a Bachelors or Master's degree in a Health Sciences-related field and had prior training on the KSADS. Consensus case conferences after the aforementioned measures were held and diagnosis was confirmed by a board-certified child and adolescent psychiatric from the clinic.

Anthropometric data was also obtained, namely height, weight and waist circumference. Height was measured with a stadiometer (Seca Inc; Chino, CA, USA), weight with a Body Mass Analysis Scale (Conair Consumer Products; Woodbridge, ON, Canada) and waist circumference with a measuring tape. BMI was calculated by dividing the weight in kilograms by the square of height in meters.

2.3.2 Diagnostic measures of mood and mood states

To define present mood, the depression rating scale (DRS) and mania rating scale (MRS) were used. The 13-item DRS has scores ranging from 0 to 67(Chambers et al., 1985). The total score of the DRS is obtained by adding the scores on 13 items: depressed

mood, irritable mood and anger, excessive guilt, anhedonia, fatigue, concentration difficulties, psychomotor agitation or retardation, insomnia, hypersomnia, increased or decreased appetite and suicidal ideation(Chambers et al., 1985). Each item is scored from 0 (no information) to 7 (very extreme), with a usual threshold score for significance of 4. The total score is obtained by adding the scores and subtracting 13. The 13-item MRS scores range from 0 to 65(Axelson et al., 2003). Items include elated and expansive mood, irritability and anger, decreased need for sleep, unusual energy level, increased activity level, grandiosity, pressured speech, racing thoughts, poor judgment, distractibility, hallucinations, delusions and mood lability(Axelson et al., 2003). Individual items are scored from 0 (no information) to 6 (extreme), with a clinical significance threshold for each individual symptom of 3 or 4 (moderate). The scoring is obtained by adding the individual scores on the 13 items, and subtracting 13.

Symptom threshold for depression and hypomania has been established as suggested and employed in previous studies (Axelson et al., 2003)(Metcalfe et al., 2016). Depression was defined as DRS ≥13(Metcalfe et al., 2016), and hypomania was defined as MRS ≥12(Axelson et al., 2003). Youth without current depression or hypomania (DRS <13 and MRS <12) were classified as euthymic BD, those with significant depressive symptoms and absence of hypomania as depressed (DRS ≥13 and MRS <12), those with significant symptoms of mania without depression (MRS ≥12 and DRS < 13) as hypomanic/manic and those with both significant depression and hypomania scores (MRS ≥12 and DRS ≥13) as mixed. The BD adolescents were then divided into three groups: hypomanic/mixed, depressed and euthymic. The decision to combine the hypomania and mixed groups was motivated by the lower number of adolescents in the pure hypomania group (n=6).

2.4 Imaging

2.4.1 Image acquisition

MRI was performed with a 3 T Philips Achieva system (Philips Medical Systems, Best, The Netherlands) using a radio frequency body coil transmission and an eight-channel head receiver coil for signal detection. The MRI protocol comprised the acquisition of T1-weighted images for anatomical registration and repeated CBF measurements using pseudo-continuous ASL. First, to plan the ASL, phase contrast angiography scout images were acquired in order to help visualize arterial and venous anatomy. The ASL images were then obtained with single shot two-dimensional EPI (TR/TE=4000/9.7 ms, 64×64×18 matrix, spatial resolution 3×3×5 mm), 1650 ms labeling duration, post-label delay of 1600 ms for the most inferior slice, 30 control-tag pairs, scan duration of 248 sec. ASL reference images were acquired with a TR=10 s to determine the initial magnetization used for quantification (Alsop et al., 2014).

Anatomical T1-weighted images were acquired using high resolution fast-field echo imaging (repetition time (TR)/echo time (TE)/inversion time (TI)=9.5/2.3/1400 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 sec).

2.4.2 ASL processing

Processing of ASL data was done using FMRIB Software Library (FSL), incorporating tools developed in the laboratory(Jenkinson et al., 2012)(MacIntosh et al., 2017). First, ASL data was co-registered 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 smoothing kernel. Difference images with large motion were removed to optimize CBF signal in grey matter (GM). The mean of the remaining images after motion correction was used to measure CBF signal(Shirzadi et al., 2015). CBF estimates were converted to absolute units (mL/100 g/min)(Alsop et al., 2015). For region of interest (ROI) analysis, standard space ROI were registered to participant ASL space, and average CBF signal within each ROI in individual participant's space was recorded.

2.4.3 Anatomical image processing

T1-weighted images were processed using FSL tools as follows: brain extractions were performed using BET for removing non-brain tissue and skull stripping(Smith, 2002). Images were co-registered to ASL space and standard space (the latter was done using the Montreal Neurological Institute whole brain template, MNI152)), with FLIRT linear registration(Jenkinson and Smith, 2001)(Jenkinson et al., 2002). Intensity normalization and segmentation of subcortical grey and white matter from extracted brains were obtained using FAST(Y. Zhang, M. Brady, 2001).

2.5 Defining regions of interest

Bilateral ROIs were selected based on regions previously found to be implicated in BD CBF studies(MacIntosh et al., 2017) (Ito et al., 1996) (Bhardwaj et al., 2010) (Drevets et al., 1997). Cortical ROIs included: ACC (anterior division of cingulate gyrus) and middle frontal gyrus (structural definition of the functional region dorsolateral prefrontal cortex (DLPFC)). Subcortical ROI included the amygdala. In addition to the three ROI, we have also investigated global GM CBF. GM global signal was based on CBF values extracted from grey matter masks previously obtained from segmentation. Cortical and subcortical

ROI were defined using parcellation from Harvard-Oxford Cortical Structural Atlas and Harvard-Oxford Subcortical Structural Atlas in FSL in 2mm standard space(Fischl et al., 2004). *FSLUTILS* commands were used to create the ROI(Fsl, 2006). Bilateral ROI masks were split using *fslinfo* and *fslmaths* commands. ROI masks were generated using *fslmaths* to add individual regions into a broader ROI. All ROI masks were thresholded at 0.25 in standard space using *fslmaths* commands.

2.6 Statistical analyses

Analyses were performed using SPSS, version 24 (IBM Corp., Armonk, N.Y., USA). Group comparisons of participants' demographic and clinical variables were assessed using one-way analysis of variance (ANOVA) and chi-square tests, as appropriate with *post hoc* pairwise comparisons in the case of significant group differences. Measures of effect sizes are presented with partial eta squared ($p\eta^2$) for continuous variables and with Cramer's V for categorical variables.

In regards to our objective to evaluate between-group differences in CBF, we used analysis of covariance models (ANCOVA) with race as covariate for each ROI. Using Bonferroni correction, the statistical significance threshold was set at p=0.017. Omnibus tests comparing ROI CBF across the groups were followed by *post hoc* pairwise comparisons of CBF, using Tukey's test. With 129 participants the model was therefore powered at 0.80 to detect a medium-large effect size (Cohen's f=0.35), with 1 covariate and α=0.017. Furthermore, our smallest cell size was of 19 participants, which restricted our power to 1 covariate.

To examine the correlation between CBF and mania and depression scores, a within-BD linear regression analysis was conducted, and included age and sex as mean-

centered covariates. Similarly, the statistical significance threshold was set at p=0.017 using Bonferroni correction. Based on a *post hoc* power calculation, the sample of 73 had 0.80 power to detect a medium effect size (Cohen's f=0.15), with 2 covariates and α=0.017.

To inform covariate selection, we have examined the composition of our sample in terms of basic demographic variables as well as factors previously found in the literature to correlate with CBF. Race, which has previously been associated with CBF (Smith et al., 2019), was the only demographic variables that differed across groups (p=0.056) and was therefore included in the between-group analyses. Age and sex were included as covariates in within-BD linear regression, as these variables are known to impact CBF (Satterthwaite et al., 2014). Despite BMI varying between the four groups (p=0.027), this was not included as a covariate as BMI has been repeatedly shown to correlate with depression and other indicators of BD severity such that it is too intertwined with the dependent variable to also be included in this study as a covariate. There were no significant differences between the three BD groups in terms of current medication or comorbidity, and these were not included in the model.

2.6 Whole brain exploratory analyses

Pairwise comparison of CBF between the four groups was also performed using a whole brain vertex wise analysis in FSL, for a total of six pair-wise comparisons. A general linear model (GLM) was used with race as covariate, employing the FLAME1 (FMRIB's Local Analysis of Mixed Effects) tool in FSL(Woolrich et al., 2004). Cluster-based thresholding was used with a voxel threshold z-value of 2.65 for a significance level of p=0.0083, using Bonferroni correction. In addition to pairwise comparisons between groups, we performed a regression analysis with a model using DRS and MRS, and age and sex as mean-centered

covariates. A z-value of 2 was used for cluster-correction, with a significance level of p=0.05. The same covariates were used for the whole brain analysis as for the ROI analysis, and the rationale for the covariates is discussed above.

3 Results

3.1 Demographic and clinical characteristics

133 adolescents were recruited, including 75 BD participants and 58 HC. Four participants were removed due to head motion artifact and insufficient image quality. Table 3 presents demographic and clinical variables for 129 adolescents, including 28 BD hypomanic/mixed, 19 BD depressed, 25 BD euthymic, and 57 HC. There were no significant differences in terms of age or sex. In four-way analysis, between-group differences in race approached statistical significance (p=0.056). Race did not however, vary between the three BD groups (p=0.245). Body mass index (BMI) varied between the groups (p=0.027), and *post hoc* pairwise comparisons found significant differences between the HC group and the BD hypomanic/mixed groups (p=0.029). The three BD groups did not vary with respect to age at BD onset, family history of BD, proportion of participants with BD-I, BD-II and BD-NOS, lifetime comorbidity or current medication (all p>0.09). Expectedly, the 4 groups were significantly different in terms of current mania and depression scores (p<0.001). The current mania scores were highest in the hypomanic/mixed group than in the HC, depressed and euthymic groups (p<0.001). Depression scores were comparable between the hypomanic/mixed group and the depressed group (p=0.23), and these groups different from the HC and euthymic groups(p<0.001). Mean CGAS scores were highest in the HC group and *post hoc* contrasts identified

significant differences between HC and the 3 BD groups(p<0.001). Significant differences were also found in terms of CGAS between BD hypomania/mixed and BD euthymic as well as between BD depressed and BD euthymic (p<0.001 and p=0.002, respectively). No other demographic or clinical variables varied significantly between groups.

Table 3. Demographic and clinical variables

	Participants				Statistics	
	HC (N=57)	BD Hypomanic/ mixed (N=28)	BD Depressed (N=19)	BD Euthymic (N=25)	F/ χ^2	P-value
Age, years	17.15±1.43	17.07±1.32	17.89±1.41	17.64±1.44	2.02	0.14
Caucasian, n (%)	32(56.1)	20(71.4)	16(88.9)	17(68)	7.56	0.056
Females, n (%)	29(50.9)	20(71.4)	10(52.6)	12(48)	3.98	0.26
SES	53.4 ±10.4	49.2±12.5	55.6±10.4	50.9±13.2	1.49	0.22
Age at onset	---	14.65±2.55	15.16±1.63	14.75±3.05	0.23	0.78
BMI	22.03±3.7[b]	24.64±5.11[a]	24.18±4.10	23.27±3.05	3.18	0.027
BD subtype (%)						
BD-I	---	9(32.1)	4(21.1)	11(44)	3.55	0.47
BD-II	---	8(28.6)	6(31.6)	8(32)		
BD-NOS	---	11(39.3)	9(47.4)	6(24)		
Lifetime comorbidity (%)						
Substance use disorder	---	9(32.1)	3(15.8)	3(12)	3.45	0.18

ADHD	---	16(57.1)	11(57.9)	8(33.3)	3.70	0.16
Anxiety disorder	---	26(92.9)	14(73.7)	17(70.8)	4.67	0.097
Family history of BD (%)	---	13(50)	11(61.1)	11(44)	1.24	0.54
Lifetime medication use (%)						
Antipsychotics	---	22(78.6)	15(78.9)	17(70.8)	0.54	0.76
Lithium	---	5(17.9)	5(26.3)	7(29.2)	0.99	0.61
Anticonvulsant	---	3(10.7)	2(10.5)	0(0)	2.75	0.25
Antidepressant (SSRI)	---	12(42.9)	7(36.8)	4(16.7)	4.28	0.12
Stimulants	---	6(21.4)	3(15.8)	6(25)	0.54	0.76
Current medication (%)						
SGA	---	20(71.4)	11(57.9)	15(60)	1.15	0.56
Lithium	---	3(10.7)	5(26.3)	7(28)	2.86	0.24
Antidepressant (SSRI)	---	5(17.9)	1(5.3)	1(4)	3.47	0.18
Stimulants	---	2(7.1)	2(10.5)	2(8)	0.16	0.92
Clinical scores (±)						
Mania score-current	0.19±0.85[b]	20.39±6.36 [a,c,d]	2.74±2.79[b]	2.28±3.78[b]	212.10	<0.001
Mania score-lifetime most severe	0.74±1.58 [b,c,d]	31.54±9.91[a]	28.47±8.97[a]	27.16±14.65[a]	115.62	<0.001
Depression score-current	0.47±1.29[b,c]	19.93±9.96[a,d]	23.32±8.04[a,d]	3.88±4.43[b,c]	113.72	<0.001
Depression score-lifetime most severe	1.53±2.69 [b,c,d]	32.44±10.99[a]	32.53±11.65[a]	26.92±11.91[a]	119.67	<0.001
CGAS – current	89.49±5.07 [b,c,d]	60.65±8.51[a,d]	61±12.42[a,d]	71.17±13.16 [a,b,c]	86.64	<0.001
CGAS – highest past	89.84±5.08 [b,c,d]	62.31±9.33[a,d]	66.26±10.8[a,d]	74.38±10.96 [a,b,c]	83.01	<0.001
CGAS – most severe	82.88±6.42 [b,c,d]	42.35±8.24[a]	43.05±8.99[a]	45.46±9.59 [a]	48.93	<0.001

Note. ADHD = attention deficit and/or hyperactivity disorder; BD = bipolar disorder; BD-I = bipolar I disorder; BD-II = bipolar II disorder; BD-NOS = bipolar disorder not otherwise specified; BMI=body mass index; CGAS=Children's Global Assessment Scale; HC=healthy controls; SES=socio economic status; SGA=second generation antipsychotic; SSRI=selective serotonin reuptake inhibitor. Subscript designates pairwise post hoc contrasts with p<0.05: a= HC; b= BD Hypomanic/mixed; c= BD depressed; d=BD euthymic.

3.2 Region of interest analyses

3.2.1 Group comparison

CBF values for the selected ROIs (amygdala, middle frontal gyrus, ACC and total GM CBF) are presented by group in Tables 4 and 5, and Figure 1. When comparing all BD to the HC, CBF differed between the two groups in the amygdala (F=4.55, p=0.035, $p\eta^2$=0.035), the ACC (F=3.93, p=0.05, $p\eta^2$=0.03), and the global gray matter (F=4.82, p=0.03, $p\eta^2$=0.037), with higher CBF in the BD group than in the HC group for all regions examined (see Table 4). These did not meet threshold for statistical significance after Bonferroni correction (p=0.017). When examining the differences between the four groups, CBF differed between groups in the ACC (F=2.80, p=0.043, η^2=0.063), although this did not meet threshold for significance after Bonferroni correction, as above. *Post hoc* pair-wise comparisons demonstrated that CBF in the ACC was higher in the BD euthymic group (77.10±2.89 ml/100g/min) than in the HC group (68.02±1.93 ml/100g/min) (p=0.062) (see Table 5, and Figure 1). No other regions examined were found to differ between the groups.

Table 4. Cerebral blood flow values in regions of interest in bipolar disorder and control adolescents

ROI	HC (n=57)	BD (n=72)	Statistics		
			F	Partial η^2	*p*
Global GM	61.42 (11.26)	65.84 (11.22)	4.82	0.037	0.03
ACC	67.93 (14.72)	73.16 (14.68)	3.93	0.03	0.05
Middle frontal gyrus	75.15 (15.23)	80.20 (15.18)	3.42	0.026	0.067
Amygdala	38.99 (10.17)	42.88 (10.14)	4.55	0.035	0.035

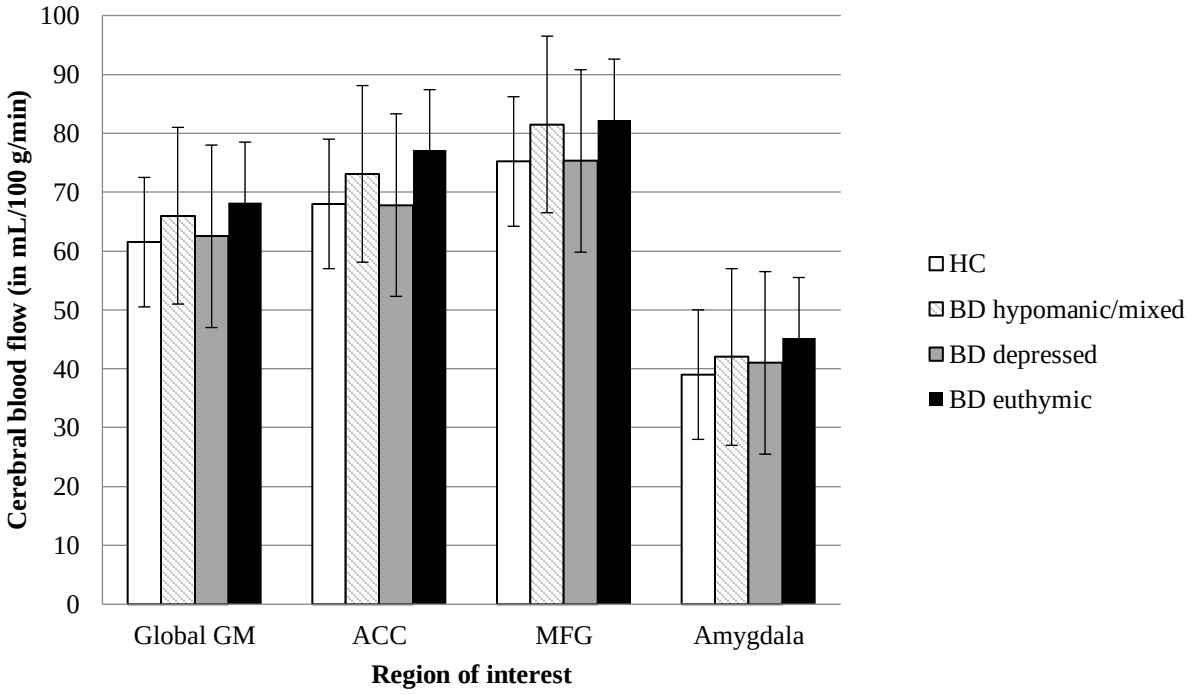
Note. CBF in ml/100 g/min (±SD)
ACC= anterior cingulate cortex; BD = bipolar disorder; CBF= cerebral blood flow; GM=gray matter; HC=healthy controls; ROI=region of interest, SD= standard deviation.

Table 5. Cerebral blood flow values in regions of interest in bipolar disorder across mood states and in control adolescents

ROI	HC (n=57)	BD hypomanic/ mixed (n=28)	BD depressed (n=19)	BD euthymic (n=25)	Statistics		
					F	Partial η^2	*p*
Global GM	61.47 (11.22)	65.91 (11.10)	62.46 (11.26)	68.22 (11.07)	2.57	0.059	0.057
ACC	68.02 (14.58)	73.08 (14.44)	67.83 (14.64)	77.10 (14.39)	2.80	0.063	0.043
Middle frontal gyrus	75.22 (15.19)	81.46 (15.03)	75.35 (15.24)	82.30 (14.98)	2.02	0.047	0.114
Amygdala	39.03 (10.17)	42.00 (10.06)	41.01 (10.20)	45.19 (10.04)	2.24	0.051	0.086

Note. CBF in mL/100 g/min (±SD)
ACC= anterior cingulate cortex; BD = bipolar disorder; CBF= cerebral blood flow; GM=gray matter; HC=healthy controls; ROI=region of interest, SD= standard deviation.

Figure 1. Cerebral blood flow in regions of interest in bipolar disorder adolescents across mood states and in control adolescents

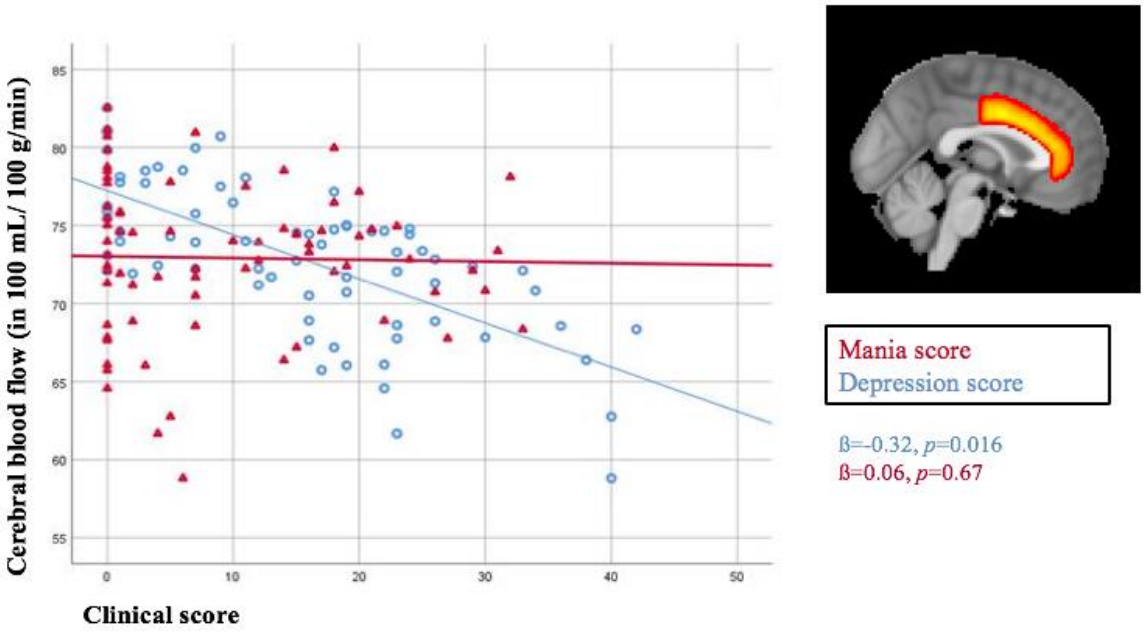


ACC= anterior cingulate cortex; BD=bipolar disorder; GM=gray matter; HC=healthy controls; MFG=middle frontal gyrus.

3.2.2 Correlation between symptoms and cerebral blood flow

Regression analyses controlling for age and sex examined the relationship between DRS and MRS, and CBF in the amygdala, middle frontal gyrus, ACC and total GM CBF. We found a negative association between DRS and ACC CBF (ß=-0.32, *p*=0.016)(see Figure 2). No other relationship was found between DRS, MRS and CBF in the ROIs examined.

Figure 2. Cerebral blood flow in the anterior cingulate cortex and clinical scores in adolescents with bipolar disorder



3.2 Whole brain-analyses

3.3.1 Group comparison

Whole brain analysis controlling for age and sex found a pattern whereby CBF was

highest in the BD euthymic group than in HC and symptomatic BD. After cluster correction, the BD euthymic group had significantly higher CBF than HC in seven clusters encompassing the left planum temporale and superior temporal gyrus, the right superior and middle temporal gyri, the left cuneal cortex and occipital pole, the right precentral gyrus and the left thalamus (see Figure 3). There was also significantly greater CBF in the euthymic BD group vs. the BD depressed and BD hypomanic/mixed group in one cluster in the left superior temporal cortex (see Figure 4). There were no significant differences between the depressed and hypomanic/mixed BD groups.

Figure 3. Regions of higher cerebral blood flow in bipolar disorder euthymic adolescents in contrast to control adolescents

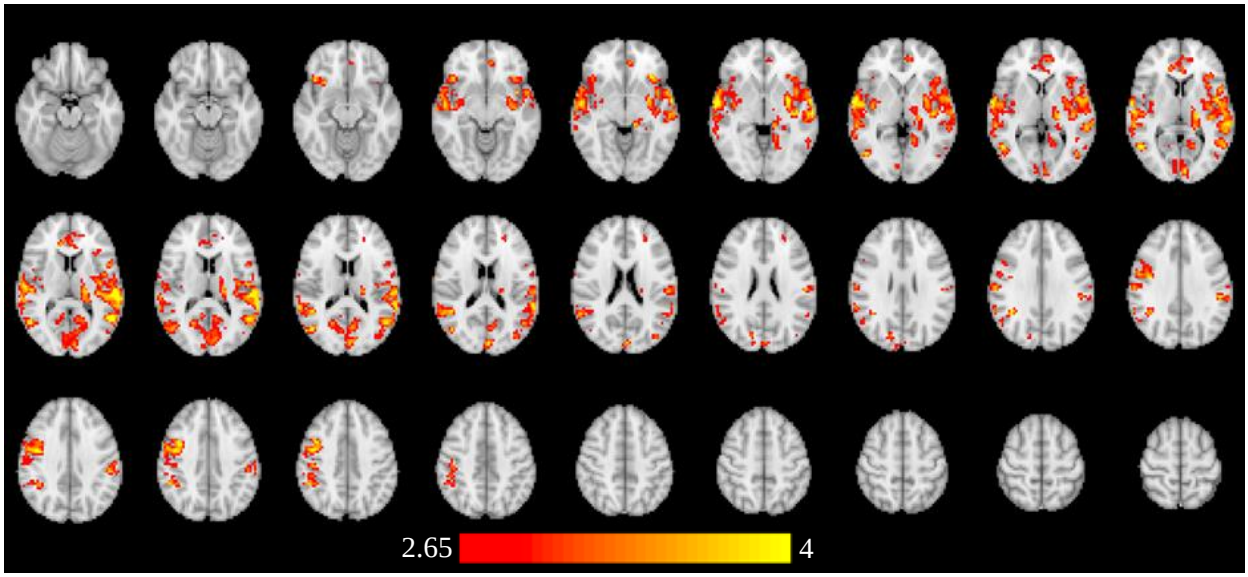
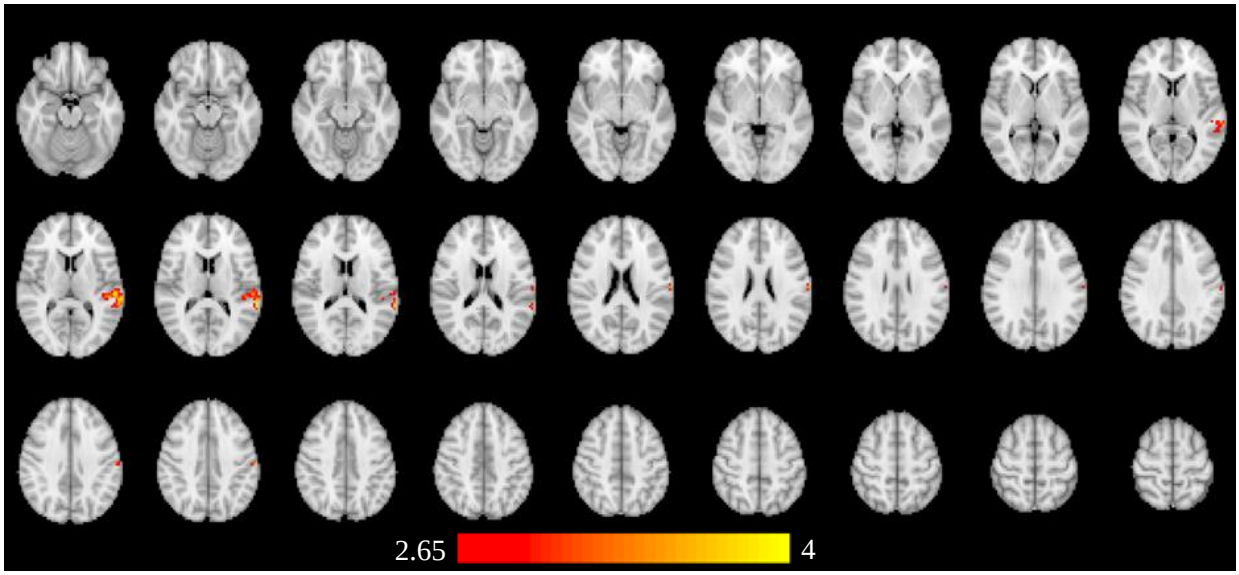


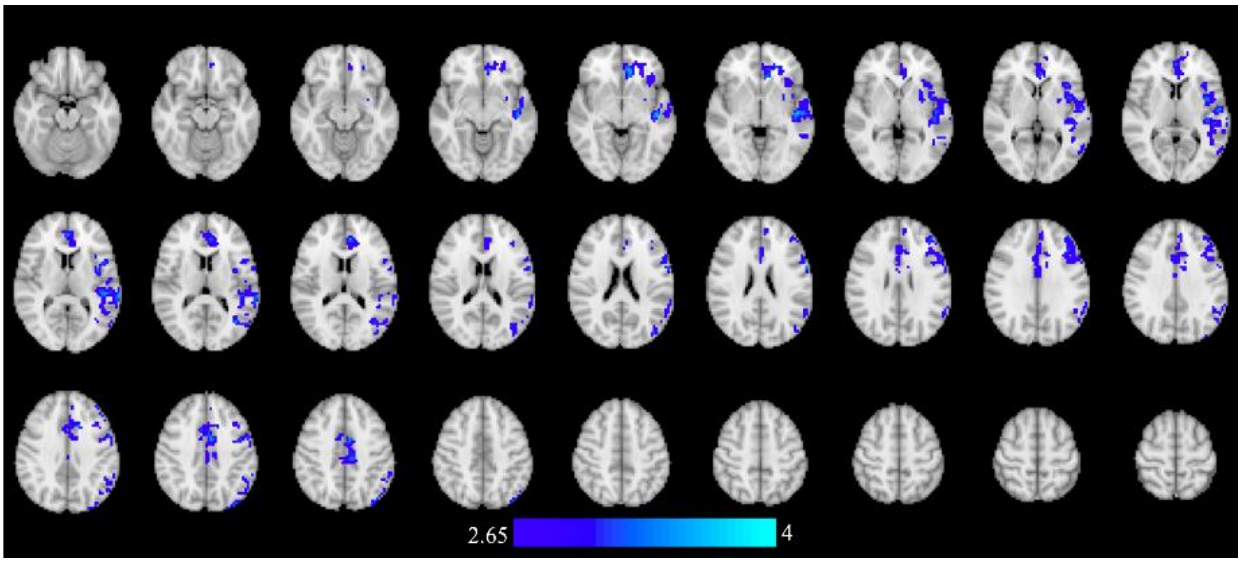
Figure 4. Regions of higher cerebral blood flow in euthymic adolescents with bipolar disorder in contrast to bipolar disorder depressed adolescents



3.3.2 Correlation between symptoms and cerebral blood flow

In the BD group, depression symptoms (DRS) were negatively associated with CBF in one cluster in the left superior temporal regions and one cluster in the left cingulate and ventromedial prefrontal cortex (VMPFC) (see Figure 5). There were no significant correlations between CBF and MRS after cluster correction.

Figure 5. Regions of negative correlation between depression severity and cerebral blood flow in adolescents with bipolar disorder



4 Discussion

4.1 Summary of findings

Investigating the link between CBF, mood episodes and severity of mood symptoms in adolescents BD, we found differences between HC, BD euthymic, BD hypomanic/mixed and BD depressed adolescents. First, we found higher CBF in the combined BD group than in HC in the amygdala, the ACC, and the global gray matter. This did not remain significant after correction for multiple comparisons. Next, when examining the differences between the symptomatic BD groups and with HC, we found a pattern of higher CBF in the ACC in the BD euthymic group, and lower CBF in the BD depressed group as well as in HC. After correction for multiple comparisons, this did not meet threshold for significance. No other region examined varied between groups. A whole brain analysis found differences in CBF between the groups in several regions. Higher CBF was identified in the BD euthymic group in contrast to HC in temporal, occipital and precentral regions and in the thalamus. Higher CBF was also found in the BD euthymic group in the left superior temporal cortex in contrast to both the BD depressed and the BD hypomanic groups. No differences were found between the BD depressed and hypomanic groups.

A regression analysis in the BD sample only examining the correlation between mania and depression scores and CBF in the aforementioned ROI identified an inverse relationship between depressive symptom severity and CBF in the ACC. On a whole brain analysis, after correction for multiple comparisons regions of negative correlation between depressive symptom severity and CBF included the left superior temporal cortex, and left cingulate and VMPFC.

4.2 Interpretation of findings

Our present results of higher CBF in BD than HC, and particularly in the BD euthymic group contrast with the findings of lower CBF in frontal and temporal regions in symptomatic BD adults in comparison to HC(Toma et al., 2018). As expected, in our ROI analysis, we identified an inverse correlation between CBF and depression scores in the ACC, but also in our whole brain analysis, in additional regions which were we had not expected such as occipital regions and the thalamus.

The following sections explore various factors which may be implicated in our findings. The impact of CBF development during adolescence, as well as of brain maturation divergences between BD and HC may explain the higher CBF in the BD group. The link between metabolism and regional CBF, and particularly the putative impact of abnormal energy metabolism and compensatory mechanisms may contribute to the finding of higher CBF in the BD euthymic group. Similarly, the absence of compensatory increase in CBF in regions implicated in emotional regulation may underlie our findings of an inverse correlation between CBF and depression scores. Finally, the interconnections between microvascular dysfunction, inflammation and abnormal energy metabolism are explored in the context of mood states in BD.

4.2.1 Neurodevelopment and cerebral blood flow

Differences in terms of CBF developmental trajectories could be implicated in the divergence between our findings and prior findings of decreased CBF in BD adults. Several studies of normal development of CBF during adolescence and young adulthood demonstrate a decline in CBF towards the end of adolescence with notable sex differences(Bray, 2017)(Biagi et al., 2007)(Chiron et al., 1992)(Satterthwaite et al., 2014).

Sex-by-age interactions in CBF development during normal adolescence were identified in regions of the heteromodal association cortex and executive network such as the posterior cingulate cortex, VMPFC, lateral temporal, and inferior parietal regions and DLPFC(Satterthwaite et al., 2014). Indeed, whereas CBF declined in mid-puberty in males, it increased in females, highlighting different processes in function of sex, possibly due to the impact of sex hormones such as estrogen(Satterthwaite et al., 2014).

Similarly, loss/pruning of gray matter volume occurs in normal adolescence and is thought to follow a characteristic inverted U-shape curve, with distinctive peak periods in various brain regions and maturation of the prefrontal cortex occurring only at the beginning of adulthood (Gogtay et al., 2004). In contrast, white matter volume and fractional anisotropy is thought to increase during adolescence (Barnea-Goraly et al., 2005)(Peters et al., 2012). Prior studies in BD adolescents have found abnormal developmental trajectories of gray and white matter volume among adolescents with BD, with putative delay in maturation (Najt et al., 2016)(Gogtay et al., 2007)(Cabeen et al., 2018)(Weathers et al., 2018).

The interplay between neurodevelopment and neuroprogression in late adolescence and early adulthood in youth with BD is not fully understood and may result in different or delayed developmental trajectories, in terms of gray matter, gray matter, functional connectivity and CBF. Hypothetically, differences in terms of developmental curves of CBF during adolescence in BD could result in higher CBF in BD as a group, either because of abnormal development of CBF curves or secondarily to white or gray matter differences. Indeed, studies in various populations report on a link between lower brain volume or lower cortical thickness and lower CBF(Appelman et al., 2008; J. J. Chen et al., 2011; Inoue et al.,

2005; Kaichi et al., 2016; Meltzer et al., 2000). A large longitudinal study in aging adults found that lower cortical thickness was predicting future decline in CBF over time, and a link between lower CBF and subsequent brain atrophy was also found in those over 65, suggesting impaired regulatory mechanisms(Zonneveld et al., 2015).

In adults with BD, there is evidence of reduced cortical thickness in comparison to healthy controls, particularly in the left ACC and paracingulate, left superior temporal regions, orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (VLPFC) and DLPFC(Hanford et al., 2016), and a recent large international study found BD cortical thinning in frontal, temporal and parietal regions, especially in the left pars opercularis, left fusiform gyrus and left middle frontal cortex(Hibar et al., 2017). Conversely, gray matter differences between adolescents with BD and controls have been less consistent, with amygdala volume reduction being the most replicated finding (Jean A Frazier et al., 2005)(Wilke et al., 2004)(Dickstein et al., 2005)(Kaur et al., 2005)(Pfeifer et al., 2008)(Kelley et al., 2013). Lower cortical volume and thickness in adults with BD could be associated with lower regional CBF in this population, which may not be captured cross-sectionally in our adolescent sample.

4.2.2 Studies of cerebral blood flow in psychiatric populations in adolescents

The literature on CBF in adolescents with mood disorders is limited. The only other study of CBF in BD adolescents reports on increased CBF in the medial frontal and middle cingulate regions using a smaller proportion of the current sample (n=31 BD and 20 HC)(MacIntosh et al., 2017). A small number of studies have investigated CBF in adolescents with major depressive disorder (MDD). A study comparing adolescents with

MDD (n=18) to healthy adolescents (n=19) with a mean age of 16.2 years old found regions of lower CBF encompassing the ACC, the cerebellum, the amygdala, the insula and inferior frontal and temporal regions, and increased CBF in the subcallosal cingulate, putamen and fusiform gyrus in the adolescents with MDD(Ho et al., 2013). No correlation was found between CBF and clinical characteristics such as severity of depressive symptoms(Ho et al., 2013). The authors conclude that their findings are overall consistent with CBF and functional imaging studies of adults with MDD, acknowledging the heterogeneity of the condition(Ho et al., 2013)(Videbech, 2000)(Pagani et al., 2004)(Lui et al., 2009).

A study of the impact of CBT on CBF in treatment naïve adolescents with MDD (mean age 16.5) found an increase in CBF in the right DLPFC, the right caudate nucleus and the left inferior parietal lobe after 5 sessions of CBT in contrast to pretreatment CBF. No link was found between symptom remission and regional CBF, which could be due to the small sample size (21 across CBT and control groups)(Sosic-Vasic et al., 2017). The authors speculate that lower CBF in cognitive executive regions may be involved in depression in adolescents, and increased CBF may be implicated in symptomatic remission(Sosic-Vasic et al., 2017).

Our findings of increased CBF in BD are consistent with those of a large transdiagnostic study in youth (age 11-23, mean age 16.1), which found increased CBF in the ACC, postcentral gyrus, medial temporal lobe and midbrain in correlation with lifetime psychopathology including mood disorders, anxiety and psychosis(Kaczkurkin et al., 2017). Furthermore, in the same sample of adolescents longstanding high levels of anxiety and mood symptoms (“trait anxiety”) were associated with increased CBF in the amygdala, anterior insula and inferior temporal cortex. In addition, higher trait anxiety was found to be

mediated by increased CBF in the amygdala in girls of post-pubertal age(Kaczkurkin et al., 2016). This is suggestive of trait increased CBF in adolescents with psychopathology in regions including the ACC, temporal and limbic regions, which is similar to our findings both in terms of regions and directionality and may represent a development-specific state.

4.2.3 Cerebral blood flow during euthymia

Our findings of state-dependent CBF differences in the BD euthymic group in contrast to the symptomatic BD groups may relate to increased neuronal activation or metabolic activity in those regions in the BD euthymic group. There is normally a coupling between CBF and activation, and increased CBF is thought to be associated with increased local neuronal activity (Paulson et al., 2009) (Villringer and Dirnagl, 1995). Furthermore, the hemodynamic response also depends on the efficacy of the energy metabolism and mitochondrial function(Kann and Kovács, 2006)(Sanganahalli et al., 2013). Studies reporting activation using blood oxygen changes (blood oxygen level-dependent (BOLD) contrast signal) as a marker of neuronal activation would be directly impacted by low CBF (Denfield et al., 2016). Indeed, fMRI BOLD results depend on CBF and on the cerebral metabolic rate of oxygen consumption (Whittaker et al., 2016). Factors influencing basal CBF levels such as caffeine or hypercapnia have been found to directly impact fMRI BOLD results (Liau et al., 2008) (Ances et al., 2008).

Our findings of increased CBF in the BD euthymic group in temporal, occipital and precentral regions as well as in the thalamus may represent a compensatory mechanism. These regions are thought to be implicated in multimodal integration of complex auditory and visual emotional information (Robins et al., 2009) (Narumoto et al., 2001) (Watson et al., 2014). fMRI studies in pediatric BD report on abnormal connectivity of the superior

temporal and visual cortices (Garrett et al., 2012)(Dickstein et al., 2010). One study reports specifically on hyperactivation of the superior temporal sulcus and fusiform gyrus in euthymic BD with emotion processing in contrast to healthy controls(Pavuluri et al., 2007).

fMRI studies in adults with BD in different mood states report on differences in amygdala activation with some reproduction of decreased activation of the prefrontal cortex across mood states(Townsend and Altshuler, 2012) (C.-H. Chen et al., 2011) (Hilary P. Blumberg et al., 2003) (R O Brady et al., 2017) (Shaffer et al., 2017) (Hummer et al., 2013) (Perlman et al., 2012) (Versace et al., 2010) (Cerullo et al., 2012). A longitudinal study comparing BD participants between mania and euthymia in a resting state paradigm found decreased connectivity between the amygdala and the anterior cingulate cortex as well as increased connectivity between the amygdala and the supplemental motor area in mania in contrast to euthymia(Roscoe O. Brady et al., 2017). A recent review of resting state connectivity in BD adults reports on heterogeneity between studies in BD euthymia in adults, with multiple studies failing to identify significant differences between default mode network, frontal parietal and salience networks between adults with BD euthymia and controls(Syan et al., 2018). Some studies included found abnormal resting state connectivity in networks encompassing the amygdala, VLPFC, cingulate and middle frontal gyrus(Syan et al., 2018). The authors report that abnormal functional connectivity of the ACC may represent compensatory mechanisms to maintain euthymia(Syan et al., 2018). Nonetheless, activation fMRI study results are challenging to interpret and compare due to different task paradigm employed and methodological differences(Weinberger and Radulescu, 2016).

Furthermore, although there is normally a coupling between brain activation and

CBF, decoupling is described in vascular and neurodegenerative disorders(Girouard, 2006; Østergaard et al., 2013). The nature of the relationship between CBF and brain activation in BD is unknown and a study in adults with BD reported on a positive correlation between metabolism and CBF in HC, and an inverse relationship between metabolism and CBF in BD in the ACC, suggesting uncoupling in a region known to have a key role in BD(Dunn et al., 2005).

Contemporary theories regarding the etiopathology of BD highlight abnormal energy metabolism and mitochondrial dysfunction(Kato and Kato, 2003)(Andreazza et al., 2018). Ineffective metabolic pathways in the context of impaired phosphorylation may lead to higher needs for CBF, in the context of higher needs for glucose and oxygen in order to maintain function(Mansur et al., 2013)(Stork and Renshaw, 2005). A study specifically found evidence of abnormal phosphorus metabolism in the frontal lobe in adolescents with BD, suggesting impaired energy metabolism(Shi et al., 2012). Therefore, maintaining euthymia may require higher CBF in adolescents with BD.

4.2.4 Cerebral blood flow in relation to severity of depressive symptoms

The inverse relationship between CBF and depression scores in the ACC, and the higher CBF in BD euthymic participants suggests that increased CBF to the ACC may be involved in euthymia and mood stability, and conversely, that low CBF in the ACC may result or originate from depressed states. The ACC is thought to be involved in the integration of emotional processing and regulation, due to its position at the intersection of ventral and dorsal prefrontal regions(Mohanty et al., 2007) (Etkin et al., 2011) (Drevets et al., 2008). Studies in both youth and adults with BD report on structural and functional abnormalities of the ACC in BD in comparison to healthy controls, although there are also

negative studies or inconsistent directionality of findings(Hirayasu et al., 1999) (Connolly et al., 2013)(Malhi et al., 2004)(Hajek et al., 2008)(Javadapour et al., 2007). Specifically, hypoactivation of the ACC in adults with BD depression has been replicated(Fountoulakis et al., 2008). 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(Diler et al., 2013). Studies in adults with BD have also linked severity of depressive symptoms with lower glucose metabolism in frontal regions(Buchsbaum et al., 1986)(Baxter Jr. et al., 1989)(Ketter et al., 2001). The directionality of these findings is unknown, i.e.: *does lower CBF in the ACC result in depressive symptoms, or do depressive symptoms lead to lower CBF in the ACC?*

4.2.5 Cerebral blood flow in relation to medication

Our results are unlikely to be solely attributable to medication, as medication was similarly distributed between the BD groups. Nonetheless, past studies have identified an impact of medication on CBF, mainly in non-BD populations, which may have impacted our contrast between BD and HC. A study in healthy volunteers found a decrease in CBF in regions encompassing the amygdala, fusiform gyrus, insula, and orbitofrontal cortex following one dose of oral citalopram(Y. Chen et al., 2011). Another study in participants with MDD found an initial higher CBF in MDD in comparison to controls in temporal and frontal regions, including the cingulate cortex, which normalized following a course of 6 weeks of treatment with escitalopram(Kaichi et al., 2016). In healthy volunteers a single dose of antipsychotics was found to increase regional CBF in the striatum, anterior cingulate and insula, and decrease CBF in frontal regions, with compound differences(Handley et al., 2013)(Hawkins et al., 2018). The only study specifically

addressing the effect of medication on CBF in BD participants examined the impact of lithium discontinuation in 14 adult BD participants and found increased CBF in the left temporal cortex and decreased CBF in the left ACC following lithium discontinuation(Goodwin et al., 1997).

Furthermore, it is important to highlight the absence of studies examining medication effects on CBF in adolescent with BD, and the presence of one study with a small sample size in adults. It is unknown if medication would impact CBF similarly in BD than in healthy controls or MDD, as discussed above.

Importantly our treatment rates are also comparable to other BD neuroimaging samples, both in adults and adolescents, and would not have impacted our sample differently(Blumberg et al., 2006)(Dickstein et al., 2005)(Chang et al., 2005). Notably however, most CBF studies in BD do not include information about participants' medication status at the time of scan(Toma et al., 2018), with some exceptions(Bhardwaj et al., 2010)(Tutus et al., 1998).

4.2.6 Cerebral blood flow, vascular pathology and inflammation

Taken together with previous findings of abnormal CBF in adults with BD, premature vascular mortality and morbidity in BD, our present findings add to the literature suggesting a link between vascular pathology and BD(Toma et al., 2018)(Fiedorowicz et al., 2014, 2012; Goldstein et al., 2015b). Here are discussed mechanistic hypotheses regarding vascular disease and BD.

Cerebral blood vessels may be abnormal in terms of structure and function in BD. Cardiovascular risk factors, known to be elevated in BD populations, are associated with aberrant pulsatility and flow velocity in large cerebral arteries, with an impact on

microcirculation(Pase et al., 2012). A large longitudinal study found that untreated hypertension in a population with atherosclerosis was associated with a decline in CBF over time, hypothesizing a link between untreated hypertension and microvascular damage, leading to lower CBF(Muller et al., 2012). Endothelial dysfunction, which is evident in adults with CVD risk factors and adults with BD, can lead to decreased availability of nitric oxide (NO), which in turn can negatively impact CBF given its involvement in CBF regulation(Davignon and Ganz, 2004; Endemann and Schiffrin, 2004; Rybakowski et al., 2006). Studies have linked low CBF and small vessel disease in the context of atherosclerosis and arteriolar lumenal narrowing leading to low CBF(Shi et al., 2016).

Furthermore, white matter hyperintensities (WMH) observed on T2 weighted MR images are often used as a marker of microvascular disease. WMH have been consistently linked with low CBF, especially in older adults(Brickman et al., 2009; van Dalen et al., 2016; Vernooij et al., 2008). WMH are also believed to be associated with endothelial dysfunction and impaired NO function(Faraci and Brian, 1994). Importantly, WMH are known to be increased in prevalence in BD subjects, which supports the possibility of an association between vascular pathology and BD(Gunde et al., 2011; Monkul et al., 2005).

Finally, a study has reported on abnormal cerebrovascular reactivity, a marker of microvascular integrity in BD adolescents, further supporting the link between BD and microvascular pathology early in the course of illness(Urback et al., 2019).

BD and CVD could be linked via increased inflammation and oxidative stress and low levels of brain-derived neurotrophic factor (BDNF)(Berk et al., 2011; Goldstein et al., 2009; Goldstein, 2017; Leboyer et al., 2012). Inflammation is associated with endovascular changes, such as impaired vasomotor function, enhanced production of reactive oxygen

species and endothelial barrier damage as well as decrease in availability of NO(Kim et al., 2013; Siti et al., 2015). Similarly, oxidative stress promotes endothelial damage via impairment of NO regulatory mechanisms(Higashi et al., 2009; Muller et al., 2007). BDNF is involved in endothelial cell proliferation and angiogenesis(Kermani and Hempstead, 2007; Liu et al., 2006), and polymorphisms in this gene have been related to abnormal cortical development specifically in mood disorders(Pezawas et al., 2008). It is hypothesized that a constellation of cardiovascular risk factors, inflammation and oxidative stress, may have a synergistic deleterious effect on the microvessels and cortex(Granger et al., 2010). Multiple studies found an increase in inflammatory markers in BD subjects, especially during mood episodes(Berk et al., 2011; Rosenblat and McIntyre, 2016).

Cerebral blood flow abnormalities in BD may be related to mood episodes. This converges with findings of increased inflammatory markers in BD during mood episodes as well as with the link between greater CVD burden and number and severity of mood episodes(Fiedorowicz et al., 2014, 2012, 2009).

4.3 Limitations

Several limitations must be acknowledged. First, our cross-sectional design did not allow the comparison of participants' mood states over time, and also precludes inferences regarding the direction of our findings (i.e. does CBF predict mood or vice versa). Similarly, due to cross-sectional design, inferences about the impact of development and developmental curve differences in BD vs HC youth cannot be tested and remains speculative. Sample size constraints required the combination of the hypomanic and mixed groups, which may represent different processes. There is no previous study of CBF in BD participants with mixed features previously. Furthermore, the manic scores in our

participants remained overall low with a limited distribution (20.39±6.36) even in our BD hypomanic/mixed group whereas the MRS is scored from 0 to 65. This is in part due to difficulties recruiting and undergoing the imaging protocol in the case of mania. This may have impacted our ability to generalize our results to participants with mania and limiting the correlation between mania scores and CBF given the limitations in distribution.

In addition, as per previously established methodology, mood scores were obtained by employing the scores of the worst week in the past month, which may in certain cases not represent mood state at the time of the imaging procedure.

Furthermore, although this was similar between BD groups, medication and comorbidity was high in our sample, as is representative of adolescent BD samples(Frias et al., 2015). This may nonetheless have impacted on our findings as medication has been found to impact CBF and brain activation as discussed above(Y. Chen et al., 2011)(Pavuluri and Passarotti, 2012). This must be balanced against the need to include a population representation of clinical samples, therefore rendering our results more generalizable.

The strengths of this study are the unique sample, representing the largest known CBF sample of BD participants irrespective of age. Given the known association between BD and CBF, there has been relatively limited study of vascular markers and integration of vascular pathology in BD imaging investigation. By including BD adolescents with a relatively narrow age range we investigated a population with a relatively recent onset of illness, limited lifetime medication use, and overall lower potential impact of neuroprogression. CBF may provide an additional useful measure to neuroimaging given its possibility for quantification, and that fMRI is representative of both CBF and neuronal activation.

4.4 Future directions

This preliminary study suggests that CBF would be worthy of ongoing study in large prospective studies to further understand BD pathophysiology and assist with treatment.

Future studies should investigate the impact of specific mood and anxiety symptoms on CBF in larger cohorts. First, larger prospective studies are warranted to examine within-person changes in CBF in relation to different mood states in BD. Linking mood symptom change and CBF changes would be interesting to note if CBF predicts changes in terms of mood or symptoms. Looking at specific symptoms of depression or hypomania such as depressed mood, irritability or changes in energy may allow to precisely identify the impact of CBF changes.

Second, studying CBF in BD at different stages of illness, including at onset and in healthy relatives may provide additional information on development of BD, in the context of known developmental factors affecting CBF development in adolescents(Satterthwaite et al., 2014).

Third, studies correlating CBF in BD with cardiovascular risk factors and peripheral inflammatory markers would also allow for testing of the hypothesis linking vascular pathology, inflammation and low CBF. Furthermore, given the impact of CBF on BOLD findings, future fMRI studies would benefit from integrating and reporting CBF as a covariate or predictor. Multi-contrast functional MRI studies are needed to further understand the complex relationship between CBF and activation. The method of choice to measure CBF depends on the patient population and the clinical question, for example ASL may be preferable in youth as it is non-invasive and does not expose participants to ionizing

radiation(Zhang et al., 2014).

Finally, despite accumulation of data regarding impaired CBF in BD, this has not been used specifically as a treatment target or treatment response marker. Future studies could evaluate CBF as a treatment target, by employing xenobiotics known to impact CBF such as nitrous oxide or pentoxifylline(McCarty et al., 2016)(Gyulai et al., 1996)(Emmanouil and Quock, 2007)(Nagele et al., 2018). CBF could also be used to characterise the response to existing treatments for BD, such as antipsychotics, mood stabilizers or antidepressants. This has not been previously studied in BD, although few studies have examined the predictive value of pre-treatment CBF in late life depression, treatment-resistant depression and OCD, with promising results(Abi Zeid Daou et al., 2017)(Richieri et al., 2011)(Wen et al., 2013). Prospective studies should assess regional CBF change in relation to treatment and response on validated symptom scales.

4.5 Conclusion

In conclusion, this controlled study of CBF differences across different mood states among adolescents with BD found state (i.e. mood-related) and trait (i.e. mood-unrelated) CBF differences. We identified higher CBF in the BD euthymic group in contrast to HC in temporal, occipital and precentral regions and in the thalamus and in contrast to the symptomatic BD in superior temporal regions. An inverse correlation between CBF and depressive symptom severity was found in the BD group in the ACC, superior temporal and VMPFC. This may further support the hypothesis of CBF compensation to ensure euthymia, and its absence, depressive symptom burden. Mechanistic hypotheses for our findings include the impact of developmental factors, differences in terms of brain

activation or structure and vascular abnormalities. This study adds to the accumulating data about the link between BD and vascular health and disease, and future directions include larger studies of CBF and BD integrating multimodal approaches and CBF as a treatment marker and target.

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Appendices

Appendix 1. Research ethics board approval

Sunnybrook
HEALTH SCIENCES CENTRE

Research Ethics Office, Room C819
2075 Bayview Avenue
Toronto, ON Canada M4N 3M5
t: 416-480-6100 ext. 4276 or 88144
www.sunnybrook.ca/reo

To: Dr. Benjamin Goldstein
Psychiatry
Room FG 53

From: Dr. Philip Hébert

Date: December 21, 2011

Subject: **Assessing Changes in Cerebral Perfusion and Neuropsychological Function in Response to Aerobic Exercise among Adolescents with versus without Bipolar Disorder**

Project Identification Number: 408-2011
Approval Date: December 21, 2011
Expiry Date: December 21, 2012

The Research Ethics Board of Sunnybrook Health Sciences Centre has conducted a Delegated Board review of the research protocol referenced above and approved the involvement of human subjects on the above captioned date. The quorum for approval did not involve any member associated with this project.

The approval of this study includes the following documents:

- Protocol dated December 19, 2011
- Informed Consent Form for Adolescents 13-19 Years of Age Version 1 dated December 19, 2011
- Informed Consent Form for Parents of Adolescents 13-19 Years of Age Version 1 dated December 19, 2011
- Recruitment Poster **(Must submit to Sunnybrook Communications & Stakeholder Relations for approval prior to posting.)**
- Study tools (received November 15, 2011):
  - General Information Sheet
  - Child and Adolescent Health Screening Report
  - Family History Score Sheet – First Degree Relatives
  - Family History Score Sheet – Second Degree Relatives
  - Family Medical History
  - K-SADS Mania Rating Scale
  - K-SADS-P Depression Section
  - Diagnostic Interview K-SADS-PL
  - K-SADS-PL Screen Interview
  - Exercise-Induced Feeling Inventory
  - PRETIE-Q

- PAR-Q
- BORG'S Rating of Perceived Exertion The 10-Point Scale
- DUSI
- Wong-Baker Faces Pain Rating Scale
- WAVE Adults/Adolescents
- Menstrual History Interview
- Tobacco Use – Lifetime
- Sleep Quality Questionnaire
- Petersen Pubertal Development Scale
- Stressful Life Events Schedule (Adolescent Self-Report)
- Stressful Life Events Schedule (Parent about Child)
- EndoPAT Booklet
- Wechsler Abbreviated Scale of Intelligence

All correspondence with the REB must include the assigned Project Identification Number. The REB requires immediate notification of all internal serious adverse events and significant deviations. Study continuation beyond one year requires submission of a renewal form prior to the expiry date or a study completion report must be received to close the file with the REB.

All REB approved studies may be subject to review by the Sunnybrook Quality Assurance and Education Program and, as Principal Investigator, you are responsible for the ethical conduct of this study. Approval by the Sunnybrook REB entails compliance with current legislation outlined in the Ontario Personal Health Information Protection Act (PHIPA) and all policies and guidelines established by Sunnybrook. All applicable contracts and agreements must be submitted to Sunnybrook Legal Services before this research may be initiated.

Philip C. Hebert, MD PhD FCFPC
Chair, Research Ethics Board
/tt

OR

Miriam Shuchman, MD
Vice-Chair, Research Ethics Board