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Increased cerebral blood flow among adolescents with bipolar disorder at rest is reduced following acute aerobic exercise

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ABSTRACT

Objective: Cerebral blood flow (CBF) is altered in mood disorders but has not been examined among adolescents with bipolar disorder (BD). Similarly, little is known about the acute neurophysiologic effects of aerobic exercise in BD. We therefore compared CBF between adolescents with and without BD at rest and acutely following a single exercise session.

Methods: Thirty-one adolescents with BD and 20 age and sex-matched controls participated in this study. CBF magnetic resonance images (MRI) were acquired using arterial spin labeling at a baseline as well as 15 and 45 min after a single 20-min session of recumbent cycling. Voxel-based CBF analyses compared groups at baseline and after exercise. Clinical, body mass index (BMI) and exercise-induced feelings inventory (EFI) data were examined for their influence on CBF findings.

Results: Baseline CBF was increased in medial frontal and middle cingulate regions in BD compared to controls. Analysis of the acute CBF changes revealed pronounced exercise-related decreases in CBF in BD. Exercise-related feelings of exhaustion were associated with CBF changes in frontal but not parietal regions.

Discussion: A single bout of moderate-intensity aerobic exercise reduced regional CBF to a greater extent in BD compared to controls; these time dependent CBF responses were associated with exercise-induced feelings of exhaustion.

1. Introduction

Bipolar disorder (BD) is a severe recurrent mood disorder that affects 2–5% of adolescents and adults (Kessler et al., 2009; Merikangas et al., 2007; Kozloff et al., 2010; Lewinsohn et al., 1995). In addition to the substantial psychiatric burden of BD, including mood symptoms and comorbid conditions such as anxiety disorders, attention deficit hyperactivity disorder, and substance use disorders (Joseph et al., 2008; Horn et al., 2011; Mann-Wrobel et al., 2011; Wingo et al., 2009; Merikangas et al., 2011; Kowatch et al., 2005), there is an enormous burden of premature and excessive cardiovascular disease (Osby et al., 2001; Weeke et al., 1987; Goldstein et al., 2009, 2015). Indeed, vascular pathology is posited as an important neurobiological underpinning of BD (Goldstein et al., 2015; Beyer et al., 2009; Gunde et al., 2011). The literature reports both within-BD group CBF differences and case-control CBF differences in cingulate regions, as determined by positron emission tomography (PET) (Kruger et al., 2006, 2003), single photon emission computed tomography (SPECT) (Benabarre et al., 2005) and arterial spin labeling (ASL) (Almeida et al., 2013). The prevailing findings among adults with BD show that CBF is decreased in medial temporal and cingulate (Culha et al., 2008), and posterior cingulate regions (Kruger et al., 2003). Importantly, CBF is also associated with mood symptoms. For example, studies have found that cingulate CBF is increased in relation to sadness, as revealed by a mood induction paradigm among adults with BD (Kruger et al., 2006, 2003). Multiple studies among adults with depression have similarly shown that CBF changes in relation to changes in depression symptoms following treatment, including pharmacotherapy, electroconvulsive therapy, vagus nerve stimulation, and transcranial magnetic stimulation (Davies et al., 2003; Phillips et al., 2015; Perico et al., 2005; Kito et al., 2008; Kosel et al., 2011).

There has been increasing interest in aerobic exercise as an

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adjunctive therapeutic approach in BD. Aerobic exercise offers cognitive benefits, reduces cardiovascular risk, and is increasingly viewed as a complementary or alternative therapy for psychiatric symptoms (Otto et al., 2007; Hillman et al., 2009; Pontifex et al., 2009). For instance, three months of aerobic exercise training was sufficient to produce a hippocampal volume increase among individuals with schizophrenia (Pajonk et al., 2010) and an increase in hippocampal cerebral blood volume in healthy adults (Pereira et al., 2007). Single bouts of aerobic exercise are clinically relevant because they can acutely improve mood processing, cognition, anxiety, and smoking cessation (Ströhle et al., 2005; Daniel et al., 2004; Tian and Smith, 2011), and because they can inform our understanding of potential mechanisms underlying the benefits of longer exercise interventions.

The current study seeks to compare regional CBF levels among adolescents with and without BD. This study also evaluates regional CBF changes after a single bout of aerobic exercise. A prior study found that adolescents with major depressive disorder had CBF differences (including regional decreases and increases) as compared to healthy adolescents (Ho et al., 2013). No prior studies have to date examined CBF among adolescents with BD. Previous studies demonstrate, however, there are neuroimaging differences between major depressive disorder (Diler et al., 2013) and BD groups (Redlich et al., 2014), which includes between-group CBF differences (Almeida et al., 2013). There are also clear neuroimaging within-BD differences by age, i.e. adolescents with BD vs adults with BD (Wegbreit et al., 2014). The current study uses ASL to quantify CBF since it is non-invasive, quantitative (Mikita et al., 2015), amenable to repeat measures and does not rely on ionizing radiation or injected contrast agents. For the first aim, we hypothesized there would be resting CBF differences between adolescents with BD when compared to controls. To characterize the resting findings, within-BD analyses were conducted on the baseline CBF levels based on clinical mania and depression scores. Further, grey matter volume was also assessed for its influence on CBF findings. For the second aim, we hypothesize that 20 min of moderate-intensity recumbent cycling exercise will elicit CBF changes that are different between the two groups. We collect CBF images once prior to exercise and twice within one hour after exercise to assess recovery. Body mass index (BMI) and self-reports from an exercise-induced feeling inventory (EFI) were considered in post hoc analyses.

2. Materials and methods

2.1. Participants

Participants with BD were recruited from a sub-specialty clinic for adolescents with BD at Sunnybrook Health Sciences Centre; healthy controls were recruited via local advertisements. Participants were males and females of any race/ethnicity between the ages of 14–19 years. The BD cohort met criteria for BD (I, II, or not otherwise specified [NOS]). Participants were excluded if any of the following applied: 1) unable to provide informed consent (e.g. severe mania or psychosis), 2) existing cardiac, auto-immune, or inflammatory condition, 3) currently taking anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, or hypoglycaemic agents including metformin, 4) infectious illness within the past 14 days, 5) contraindications to MRI, 6) health condition or physiological impairment that would preclude participation in exercise (e.g. resting blood pressure > 160/100, musculoskeletal impairments that could worsen with exercise), 7) neurological impairment, autism, and/or IQ < 80. Participants and their parent/guardian provided written informed consent. The Sunnybrook Research Ethics Board approved this study. A total of 31 adolescents with BD and 20 control adolescents were enrolled, group matched for age and sex. The former group consisted of 10 with BD-I, 10 with BD-II, and 11 with BD-NOS, as determined by the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997).

Table 1
Demographic and clinical characteristics.

Adolescents	With BD	Without BD	Group difference
N	31	20	
Sex, M/F	22/9	8/12	n.s.
Age, years mean (SD)	16.9 (1.4)	16.2 (1.7)	n.s.
Age of BD onset, years mean (SD)	14.0 (2.9)	n.a.	
Caucasian race	28	15	n.s.
BMI, mean (SD)	24.0 (3.4)	20.8 (2.7)	p=0.003
Right handed (%)	83%	76%	
SBP, mean (SD)	132.4 (19.3)	123.7 (19.0)	n.s.
DBP, mean (SD)	72.0 (18.4)	72.2 (14.3)	n.s.
BD subtype (I/II/NOS)	10 / 10 / 11	–	
BD age of onset, mean (SD)	14.4 (2.4)	–	
Antipsychotic prescription	23	–	
Mania total score	9.9 (9.1)	–	
Depression total score	14.4 (11.1)	–	
CGAS	61 (11)	90 (4.0)	
Current illness phase			
Hypomania	5	–	
Depression	8	–	
Mixed	8	–	
Euthymic	10	–	

Abbreviations: SD=standard deviation, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, BD=Bipolar Disorder, CGAS=Children's Global Assessment Scale.

2.2. Clinical procedure and measures

Current and lifetime diagnoses were determined with the KSADS-PL, incorporating information from BD adolescents and their parent or guardian. The KSADS DEP-P (Chambers et al., 1985) and KSADS Mania Rating Scale (MRS) (Axelson et al., 2003) were substituted for the mood sections of the KSADS-PL. All interviewers had completed a bachelor's or master's degree in a health science field and underwent KSADS training under the supervision of the senior author (B.G.). BD-I and BD-II were diagnosed using DSM-IV criteria. BD-NOS was operationally defined using criteria from the Course and Outcome of Bipolar Youth (COBY) study (Birmaher et al., 2006) as follows: (i) two DSM-IV manic symptoms (three if only irritable mood is reported), (ii) change in functioning, (iii) mood and symptom duration of at least four hours during a 24-h period, and (iv) at least four cumulative 24-h periods of episodes that meet the mood, symptom, and functional change criteria over the participant's lifetime.

Interviewers also administered the Children's Global Assessment Scale (CGAS), which indicates participants' level of general functioning (Shaffer et al., 1983), and the Family History Screen (with parents and adolescents) to identify the psychiatric status of first- and second-degree relatives (Weissman et al., 2000). After the interview was completed using the aforementioned measures, consensus conferences were held with a child-adolescent psychiatrist (B.G.) for diagnostic confirmation.

Height and weight were measured in light clothing to the nearest 0.5 cm and 0.1 kg, respectively, using a Tanita scale and separate stadiometer, in accordance with the National Health and Nutrition Examination (NHANES) anthropometry procedures manual (National Health and Examination Survery (NHANES) Anthropometry Procedures Manual, 2007). Weight was adjusted according to clothing (1.4 kg for long pants and long shirt/sweatshirt, 1.1 kg for short pants or short-sleeves, and 0.9 kg for both short pants and short-sleeves). BMI was calculated as weight in kilograms divided by square of height in meters. Systolic and diastolic blood pressure was measured using an