Journal of Affective Disorders 218 (2017) 227–237

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Retinal photography: A window into the cardiovascular-brain link in adolescent bipolar disorder

Melanie R. Naiberg[a,c,h], Jessica K. Hatch[a,c,h], Beth Selkirk[d,h], Lisa Fiksenbaum[a,h], Victor Yang[b,e,h], Sandra Black[b,e,f,h], Peter J. Kertes[d,g,h], Benjamin I. Goldstein[a,c,h,*]

[a] Sunnybrook Health Sciences Centre, Centre for Youth Bipolar Disorder, Toronto, Canada
[b] Sunnybrook Research Institute, Hurvitz Brain Sciences Research Program, Toronto, Canada
[c] University of Toronto, Department of Pharmacology and Toxicology, Toronto, Canada
[d] The John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, Department of Ophthalmology and Vision Sciences, Toronto, Canada
[e] University of Toronto, Department of Neurosurgery, Toronto, Canada
[f] Sunnybrook Health Sciences Centre, Department of Medicine (Neurology), Toronto, Canada
[g] University of Toronto, Ophthalmology and Vision Sciences, Toronto, Canada
[h] Univeristy of Toronto, Department of Neurology, Toronto, Canada

ARTICLE INFO

Keywords:
Bipolar disorder
Adolescents
Cardiovascular disease
Retinal photography
Mood disorders

ABSTRACT

Objective: The burden of cardiovascular disease in bipolar disorder (BD) exceeds what can be explained by traditional cardiovascular risk factors (CVRFs), lifestyle, and/or medications. Moreover, neurocognitive deficits are a core feature of BD, and are also related to CVRFs. We examined retinal vascular photography, a proxy for cerebral microvasculature, in relation to CVRFs, peripheral microvascular function, and neurocognition among BD adolescents.

Methods: Subjects were 30 adolescents with BD and 32 healthy controls (HC). Retinal photography was conducted using a Topcon TRC 50 DX, Type IA camera, following pupil dilation. Retinal arteriolar and venular caliber was measured, from which the arterio-venular ratio (AVR) was computed. All measures were conducted masked to participant diagnosis. Peripheral arterial tonometry measured endothelial function. Neurocognition was assessed using the Cambridge Neuropsychological Tests Automated Battery.

Results: AVR was not significantly different between groups (Cohen's $d = 0.18$, $p = 0.103$). Higher diastolic blood pressure (BP) was associated with lower (worse) AVR in BD ($r = -0.441$, $p = 0.015$) but not HC ($r = -0.192$, $p = 0.293$). Similarly, in the BD group only, higher (better) endothelial function was associated with higher AVR ($r = 0.375$, $p = 0.041$). Hierarchical regression models confirmed that, independent of covariates, retinal vascular caliber was significantly associated with diastolic BP and endothelial function in BD. Within the BD group, mood scores were significantly negatively correlated with AVR ($\beta = -0.451$, $p = 0.044$).

Limitations: This study's limitations include a small sample size, a cross-sectional study design, and a heterogeneous sample.

Conclusion: Retinal photography may offer unique insights regarding the cardiovascular and neurocognitive burden of BD. Larger longitudinal studies are warranted.

1. Introduction

Bipolar disorder (BD) is an impairing mood disorder that is prevalent in approximately 2–5% of adolescents (Kessler et al., 2009; Kozloff et al., 2010; Van Meter et al., 2011). Adolescent-onset BD is accompanied by greater episodicity, symptom severity, comorbidity, functional impairment, and diagnostic delay, as compared to adult-onset BD (Carter et al., 2003; Freeman et al., 2009; Goldstein and Levitt, 2006; Leverich et al., 2007; Rademacher et al., 2007). Beyond the mood symptoms that comprise BD, studies of adults and adolescents with BD have demonstrated an increase in cardiovascular disease (CVD), cardiovascular risk factors (CVRFs) and neurocognitive deficits, problems which both persist into adulthood (Dev and Eyler, 2016; Dickstein et al., 2007; Fagiolini et al., 2005; Fiedorowicz et al., 2008; Goldstein et al., 2015a, 2008, 2015b; Kemp et al., 2014; Naiberg et al., 2016a, 2016b; Robinson et al., 2006). In terms of neurocognitive impairment, studies have shown impairment in attention, memory, emotional face processing, and cognitive flexibility in adolescent BD

* Correspondence to: Sunnybrook Health Sciences Centre, Toronto, ON, Canada M4N 3M5.
E-mail address: benjamin.goldstein@sunnybrook.ca (B.I. Goldstein).

http://dx.doi.org/10.1016/j.jad.2017.04.066
Received 27 February 2017; Received in revised form 21 April 2017; Accepted 28 April 2017
Available online 29 April 2017
0165-0327/

(Adleman et al., 2011; Brotman et al., 2009; Dickstein et al., 2016, 2007, 2004a; Gorrindo et al., 2005; McClure et al., 2005; Passarotti et al., 2010; Pavuluri et al., 2006, 2009, 2010; Rich et al., 2008). In a review article on this topic, which included 757 children and adolescents, the following neurocognitive domains were impaired: verbal memory, working memory, processing speed, executive function, visual memory, and verbal fluency (Horn et al., 2011). Importantly, neurocognitive deficits remain present during euthymic phases of BD, specifically in verbal learning, verbal memory, working memory, visual learning, and visual memory (Elias et al., 2017). The current study focuses on a response reversal cognitive flexibility task that has yielded replicated findings in pediatric BD and has been linked with vascular variables. A number of studies have consistently found reduced cognitive flexibility among adolescents with BD (Adleman et al., 2011; Clark et al., 2001; Dickstein et al., 2010a, 2010b, 2005, 2007, 2004b; Gorrindo et al., 2005; Wegbreit et al., 2016, 2013). Compared to HCs, adolescents with BD demonstrate increased errors on reversal stages of cognitive flexibility tasks, slower adaptation to accurate stimuli, and are less likely to meet learning criterion (Dickstein et al., 2010b, 2007; Gorrindo et al., 2005; Wegbreit et al., 2016). Reversal learning is mediated by the same frontostriatal circuit that plays a role in BD (Blumberg et al., 2002; Drevets, 2000; Krain et al., 2008; Monk et al., 2006; Pfeifer et al., 2008; Thomas et al., 2001). In a neuroimaging study involving youth with BD, those with BD had greater neural activity in the dorsomedial frontal cortex, the lateral superior frontal cortex, and the parietal cortex during reversal stages of a cognitive flexibility task compared to HCs (Dickstein et al., 2010b).

Moreover, prior studies have also found that cognitive flexibility and other executive functions are associated with CVRFs and endothelial function (Naiberg et al., 2016b, 2016c; Newton et al., 2016; Yau et al., 2014). For example, in a systematic review that included 10 articles, executive function was shown to be consistently associated with endothelial function among healthy individuals (Naiberg et al., 2016c). Furthermore, among BD adolescents, triglyceride levels and diastolic blood pressure (BP) have been shown to be associated with deficits in cognitive flexibility (Naiberg et al., 2016b). Retinal vascular caliber, which is a proxy for cerebral microvasculature, may help to better understand these features of BD.

Retinal microvessels are arguably the best available proxy measure of cerebral microvessels for three main reasons. First, retinal microvessels can be non-invasively visualized and measured directly (Heringa et al., 2013; Meier et al., 2013). Second, retinal microvasculature shares anatomic, embryologic and physiologic characteristics, and similar autoregulation properties, with cerebral microvasculature (Kwa, 2006; Patton et al., 2005; Shalev et al., 2013; Wong et al., 2001a, 2001b). Retinal and cerebral vessels have a common embryologic origin, similar size (40–200 μm), structure, and functional barriers (i.e. the blood-brain/blood-retinal barrier) (Lloyd et al., 1995; Wong and Mitchell, 2007). Third, retinal microvascular pathology is associated with cerebral small-vessel disease and predicts future clinical stroke (Doubal et al., 2009; Hilal et al., 2014; Ikram et al., 2006; Kawasaki et al., 2012; Kwa et al., 2002; Wong et al., 2001a). Retinal photography therefore offers an opportunity to non-invasively investigate cerebral vasculature. Retinal vascular caliber has not yet been studied in a BD population; however, psychiatric symptoms and diagnoses, including depression and schizophrenia, are associated with poor retinal vascular caliber (Ikram et al., 2010; Meier et al., 2014, 2013).

Poor retinal vascular caliber (wider retinal venules and/or narrower retinal arterioles) are associated with CVRFs in healthy adults and adolescents (Gopinath et al., 2011a; Gopinath et al., 2011b; Murgan et al., 2013; Newman et al., 2016; Wong et al., 2006). In healthy adults, retinal vascular caliber is indicative of overall vascular health; narrower retinal arterioles are associated with higher BP and greater body mass index (BMI), and wider retinal venules are associated with diabetes, greater BMI, high levels of glucose, triglycerides, and low-density lipoprotein (LDL)-cholesterol, and low levels of high-density lipoprotein (HDL)-cholesterol (Liew et al., 2008; Ogagarue et al., 2013; Wong et al., 2006). Importantly, retinal vascular caliber predicts CVD independent of CVRFs (Wong et al., 2001b; Wong and Mitchell, 2004). Another question that arises when attempting to understand the relevance of retinal vascular measures is how they relate to peripheral vascular measures. Although less studied in relation to retinal vessels than traditional CVRFs, there is evidence that peripheral endothelial dysfunction is associated with wider retinal venular caliber in adults (Nguyen et al., 2010). Integrating endothelial function alongside retinal vascular measures offers to increase understanding of the importance of vascular measures in relation to cognition, mood, and CVRFs.

In healthy adolescents, narrower arteriolar caliber and wider venular caliber are associated with higher systolic and diastolic BP, and greater BMI (Gopinath et al., 2011a, 2011b; Murgan et al., 2013; Newman et al., 2016). No prior studies have determined the relationship between retinal vascular caliber and endothelial function among adolescents, or among patients of any age group with BD.

The link between retinal vascular caliber and neurocognition has been established in middle-aged and elderly adults, among whom poorer neurocognitive performance is associated with narrower central retinal arteriolar equivalent (CRAE) and wider central retinal venular equivalent (CRVE) (de Jong et al., 2011; Shalev et al., 2013). A large review consisting of 32 studies and 30,601 aging adults ($\geq$50 years old) concluded that poorer performance in several neurocognitive domains, including attention and executive functioning, processing speed, and memory, is associated with poorer retinal vascular caliber (Heringa et al., 2013). Large-scale longitudinal studies demonstrate that narrower CRAE is associated with an increased risk of vascular dementia (de Jong et al., 2011) and that, even in healthy adults, wider CRVE was associated with poorer performance on tasks of verbal comprehension, perceptual reasoning, working memory, processing speed, executive functioning, memory, and motor functions, after controlling for lifestyle and environmental factors (Shalev et al., 2013). No prior studies have determined the relationship between retinal vascular caliber and neurocognition among adolescents, or among patients of any age group with BD.

Despite the promising findings summarized above, there are important gaps in the literature relating to retinal vascular photography. This pilot study aims to determine the association of retinal vascular caliber with CVRFs and endothelial function, and the association of retinal vascular caliber with neurocognition, among adolescents with BD and healthy controls (HC). The outcomes of this study will help to determine if differences in cerebral microvasculature, using retinal vascular photography as a proxy, underlie these two core features of BD. We hypothesized that narrower CRAE and wider CRVE will be associated with greater metabolic syndrome (MetS) components (increased triglycerides, systolic and diastolic BP, glucose, and waist circumference, and decreased HDL cholesterol), poorer endothelial function, and poorer frontal-executive neurocognitive task performance. We hypothesized that frontal-executive neurocognitive tasks would yield the most significant findings, as this is the cognitive domain that has been most robustly associated with both BD and CVRFs (Dickstein et al., 2007; Naiberg et al., 2016b, 2016c). Furthermore, we hypothesized that in hierarchical regression models, findings would remain significant after controlling for relevant covariates. These analyses were performed in order to obtain a measure of contribution of each independent variable to the outcome of the dependent variable. Exploratory analyses examined the associations of other CVRFs, additional neurocognitive domains, BMI, and mood symptoms with retinal vascular measures. BMI measures were included as exploratory as waist circumference, included in the main analyses, is a better measure of abdominal obesity.