Brain and Cognition 124 (2018) 1–13

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Using an emotional saccade task to characterize executive functioning and emotion processing in attention-deficit hyperactivity disorder and bipolar disorder

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ARTICLE INFO

Keywords:
Attention-deficit hyperactivity disorder
Bipolar disorder
Antisaccade
Executive functioning
Emotion processing

ABSTRACT

Despite distinct diagnostic criteria, attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) share cognitive and emotion processing deficits that complicate diagnoses. The goal of this study was to use an emotional saccade task to characterize executive functioning and emotion processing in adult ADHD and BD. Participants (21 control, 20 ADHD, 20 BD) performed an interleaved pro/antisaccade task (look toward vs. look away from a visual target, respectively) in which the sex of emotional face stimuli acted as the cue to perform either the pro- or antisaccade. Both patient groups made more direction (erroneous prosaccades on antisaccade trials) and anticipatory (saccades made before cue processing) errors than controls. Controls exhibited lower microsaccade rates preceding correct anti- vs. prosaccade initiation, but this task-related modulation was absent in both patient groups. Regarding emotion processing, the ADHD group performed worse than controls on neutral face trials, while the BD group performed worse than controls on trials presenting faces of all valence. These findings support the role of fronto-striatal circuitry in mediating response inhibition deficits in both ADHD and BD, and suggest that such deficits are exacerbated in BD during emotion processing, presumably via dysregulated limbic system circuitry involving the anterior cingulate and orbitofrontal cortex.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) are two prevalent psychiatric conditions which pose significant health, social, and economic burden to those affected. ADHD is a neurodevelopmental disorder characterized by persistent symptoms of inattention and/or hyperactivity and impulsivity that present in early childhood and often continue into adulthood (American Psychiatric Association [APA], 2013; Faraone et al., 2000). BD is a mood disorder involving abnormal fluctuations in mood, energy, and cognition during episodes of hypomania, mania, and depression, with diagnosis typically occurring in early adulthood (APA, 2013; Grande, Berk, Birmaher, & Vieta, 2016). Despite distinct differences in age of onset (childhood in ADHD vs. adolescence/early adulthood in BD) and disease course (persistent symptoms in ADHD vs. episodic symptoms in BD) (Brus, Solanto, & Goldberg, 2014), both disorders share cognitive (Michelini et al., 2016; Torralva et al., 2011) and emotion (Richard-Lepouriel et al., 2016) processing deficits, which, together with overlapping symptomology, make differential diagnoses challenging for clinicians. Our ability to distinguish the symptomology of ADHD and BD, as well as to understand their underlying mechanisms, is limited by a lack of valid behavioral biomarkers that support clinical assessment and diagnosis.

Impairments in executive functioning skills such as response inhibition have been described as central to both ADHD (Nigg, 1999, 2001; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and BD (Bora, Yucel, & Pantelis, 2009; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009), and have been linked to dysfunction in fronto-striatal circuitry, including areas such as the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), inferior frontal cortex, basal ganglia, and thalamus (Aron, 2011; Blumberg & Leung, 2003; Hakvoort Schwerdtfeger et al., 2013; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Strakowski, DelBello, & Adler, 2005). Similarly, both disorders face difficulties in the identification and processing of emotional stimuli (De Brito Ferreira Fernandes et al., 2016; Degabriele, Lagopoulos, & Malhi, 2011; Ibáñez et al., 2011; Miller, Hanford,

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https://doi.org/10.1016/j.bandc.2018.04.002
Received 20 November 2017; Received in revised form 11 April 2018; Accepted 15 April 2018

Fassbender, Duke, & Schweitzer, 2011), and have been shown to exhibit hyperactivation in regions of the limbic system such as the amygdala (Brotman et al., 2010, 2014; Keener et al., 2012; Posner et al., 2011), a structure crucial in the perception of emotionally salient information, face emotion processing, and fear conditioning (Anderson & Phelps, 2001; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; LeDoux, 2009). Although executive functioning and emotion processing deficits have been characterized in each disorder independently, few studies have directly compared ADHD and BD on the basis of both of these deficits during a single task paradigm, making it unclear as to whether they can be used to quantitatively differentiate the two disorders from one another. For example, response inhibition deficits have been reported to differentiate both ADHD and BD groups from healthy controls, but not from one another (Michelini et al., 2016), and emotion dysregulation has also been reported to differentiate both groups from healthy controls, with BD individuals scoring higher on scales of emotional lability, and ADHD individuals scoring higher on scales of emotional responsiveness (Richard-Lepouriel et al., 2016). Behavioral and functional imaging studies have provided insight into the complex relationship between cognitive control and emotion processing, and how their interaction is crucial in mediating goal-directed behavior. Emotion processing has been positively associated with several core domains of cognitive functioning (Mathersul et al., 2009), and executive functioning has been shown to have a direct relationship with aspects of social cognition such as theory of mind (Ahmed & Miller, 2011). Furthermore, studies which probe both processes simultaneously have demonstrated reciprocal relationships whereby emotion processing is critically dependent on the availability of cognitive processing resources, and vice-versa (Cohen, Moyal, & Henik, 2015; Jasinska, Yasuda, Rhodes, Wang, & Polk, 2012; Kalanthroff, Cohen, & Henik, 2013; Schupp et al., 2007). These emotion-cognition interactions have been suggested to be mediated by fronto-limbic networks which include the dlPFC, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and amygdala (Hariri, Bookheimer, & Mazziotta, 2000; Mériau et al., 2006; Rolls, 2004; Shafritz, Collins, & Blumberg, 2006). Dysregulation in the circuitry connecting the dlPFC, ACC, and OFC with the striatum and thalamus have been hypothesized to cause executive dysfunction, impulsivity, and emotional lability associated with a number of psychiatric disorders (Bonelli & Cummings, 2007), and in ADHD and BD may contribute to an emotional bias in inhibitory control (Hummer et al., 2013; Schulz et al., 2014). It is evident that a direct comparison of ADHD and BD using paradigms which probe the functionality of executive functioning and emotion processing circuits, as well as their validity to serve as behavioral biomarkers, is necessary.

Eye tracking provides a sensitive means of establishing behavioral biomarkers through assessment of both executive functioning and emotion processing. The interleaved pro/antisaccade task requires participants to generate either a prosaccade toward a peripheral target, or instead suppress this automatic response and generate a voluntary antisaccade away from a peripheral target. This task requires recruitment of the dlPFC, frontal (FEF), supplementary (SEF), and parietal (PEF) eye fields, basal ganglia, and thalamus (Munoz & Everling, 2004), and provides insight into executive functioning in a range of neurological disorders (Coe & Munoz, 2017; Gooding & Basso, 2008; Reilly et al., 2014). An increased percentage of direction errors (erroneous prosaccades when an antisaccade was cued) and longer saccadic reaction time (SRT; time from target appearance to saccade initiation) are indicative of deficits in response inhibition and processing speed, and have been demonstrated in both ADHD (Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Hakvoort Schwerdtfeger et al., 2013; Munoz, Armstrong, Hampton, & Moore, 2003; Nigg, Butler, Huang-Pollock, & Henderson, 2002) and BD (Gooding & Tallent, 2001; Harris, Reilly, Thase, Keshavan, & Sweeney, 2009; Malsert et al., 2013; Martin et al., 2007; Soncin, Brien, Coe, Marin, & Munoz, 2016). We recently developed an emotional pro/antisaccade task in which emotional face stimuli were presented simultaneously with a central colored cue that instructed either a pro- or antisaccade to be made (Soncin et al., 2016). ADHD participants made more direction errors on antisaccade trials in this task than healthy controls, and BD participants had longer reaction times following the presentation of negatively and neutrally valenced stimuli. While these findings support the use of an emotional pro/antisaccade task as a novel method to compare executive functioning and emotion processing in ADHD and BD, emotional face stimuli were task irrelevant in this paradigm, and therefore may have limited the behavioral responses elicited in both patient groups.

The goal of this study is to characterize executive functioning and emotion processing in adult ADHD and BD using an optimized version of the emotional pro/antisaccade task. We seek to extend upon the findings reported by Soncin et al. (2016) by investigating both macrosaccade and microsaccade behavior. Microsaccades are tiny eye movements which behave similarly to larger saccades (Zuber, Stark, & Cook, 1965), and prevent perceptual fading during prolonged visual fixation (Martinez-Conde, Macknik, Troncoso, & Dyar, 2006). Microsaccades are reflective of action preparation (Watanabe, Matsuo, Zha, Munoz, & Kobayashi, 2013), covert attention (Engbert & Kliegl, 2003; Hafed & Clark, 2002), and emotion processing (Kashihara, Okanoya, & Kawai, 2014), and may therefore provide another behavioral biomarker to distinguish ADHD from BD. Here, we use a paradigm in which the sex (male or female) of emotional face stimuli acts as the instructional cue to perform either the pro- or antisaccade. Given that sex can be discriminated quickly (Mouchetant-Rostaing, Giard, Bentin, Aguera, & Pernier, 2000) and in the presence of other task demands (Reddy, Wilken, & Koch, 2004), we anticipate that by making face stimuli task relevant, patient groups will be more susceptible to emotional valence. This is different from our previous paradigm in which centrally presented colored cues conveyed trial instruction and all face stimuli were task irrelevant. We hypothesize that executive functioning, as assessed by antisaccade task performance (Coe & Munoz, 2017), will differentiate patient groups from controls, while emotion processing, as assessed by performance on trials of different face stimuli valence, will further differentiate patient groups from one another.

2. Materials and methods

2.1. Participants

This study was approved by the Queen's University Human Research Ethics Board, and was in accordance with the Canadian Tri-council Policy Statement on Ethical Conduct for Research Involving Humans and the principles of the Declaration of Helsinki. All participants gave informed consent and were compensated for their time. Initially, 25 healthy controls, 21 ADHD, and 24 BD individuals were recruited for this study. Control participants were sex- and age-matched to patient participants. From the control group, 4 participants were excluded; 1 for not meeting the inclusion criteria for a control participant, 2 for having antisaccade direction error percentages greater than 3 interquartile ranges above the upper quartile of the data, and 1 for poor quality of eye tracking data due to fatigue. From the ADHD group, 1 participant was excluded for poor quality of eye tracking data due to head movement. From the BD group, 4 participants were excluded; 1 for having a subsequent diagnosis of Parkinson's disease, 1 for poor quality of eye tracking data (40% of trials lost), and 2 for being unable to complete the testing due to fatigue. A final analysis was therefore conducted for 21 control (mean age = 37.05, range = 20–68, 11 male), 20 ADHD (mean age = 35.85, range = 19–64, 9 male), and 20 BD (mean age = 37.85, range = 22–72, 11 male) participants (Table 1).

ADHD and BD participants were recruited from the Adult Outpatient Clinic at Hotel Dieu Hospital in Kingston, Canada. To be eligible, patients had to meet DSM-V criteria (APA, 2013) for a diagnosis of either ADHD or BD. Given the high frequency of anxiety disorders in both ADHD (Kessler et al., 2006) and BD (Simon et al., 2004) in adulthood, patients with co-morbid life time anxiety disorders were