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

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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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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

Table 1
Demographic information of sex, age, and level of education for the 3 participant groups.

	Control	ADHD	BD
n (Male)	21 (11)	20 (9)	20 (11)
Mean age (SD)	37.05 (14.82)	35.85 (14.02)	37.85 (16.09)
Level of Education (n)	High school (2), College (3), Undergraduate (9), Graduate (3), Professional (4)	High school (2), College (10), Undergraduate (6), Graduate (1), Professional (1)	High school (4), College (8), Undergraduate (5), Graduate (2), Professional (0)

included in this study. Patients meeting the criteria for any other comorbid psychiatric disorders were excluded, and patients additionally could not meet the criteria for both ADHD and BD. Patient recruitment and screening was performed by psychiatrist and project co-author AM. Control participants were recruited through newspaper and online advertisements, and underwent screening for psychiatric conditions by the same psychiatrist using the MINI International Neuropsychiatric Interview (MINI 5.0; Sheehan et al., 1998). To be eligible, control participants could not meet the criteria for a psychiatric condition. ADHD participants were asked to refrain from taking their stimulant medication on the day that they were being tested. In order to maintain euthymic mood state, BD participants continued to take their mood stabilizer medication during testing, and were scheduled for testing within a week of their most recent clinical assessment.

2.2. Experimental protocol

Following screening, participants completed the emotional pro/antisaccade task. Participants were seated in a dark room approximately 60 cm away from a 17 in. computer screen with a 1280 × 1024 pixel resolution. An infrared camera-based eye tracker (Eyelink 1000; SR Research Ltd, Ottawa, ON, Canada) was used to track monocular eye position at a sampling rate of 500 Hz. A 9-point array calibration was performed for each participant prior to beginning the task. Each trial (Fig. 1A) began with the presentation of a central gray fixation cross (67 cd/cm^2, 0.5° in diameter) for a uniform random distribution of 500–900 ms, which was then replaced with a grayscale face stimulus (341 × 512 pixel image, 8.4° × 12.6°). Face stimuli were taken from the Radboud Faces Database (www.rafd.nl) and were validated previously for the accuracy of the emotions expressed (Langner et al., 2010). Face stimuli were normalized for luminance (average luminance 20 cd/m^2, maximum luminance 57 cd/m^2), size, and position, with eyes and noses aligned across all images. On each trial one of six possible face stimulus types was presented: happy, neutral, sad, fearful, angry, or a face void of any facial features (no face) that acted as a control stimulus (Fig. 1B). For no face stimuli, facial features (eyes, nose, and mouth) were blurred out, while the hair and outline of the faces were unchanged to ensure that sex discrimination was still possible for correct task completion. Participants were instructed that the sex of the face would be the cue to perform either a pro- or antisaccade to a target appearing 10° to the left or right of the face after 600 ms time.

Each participant was given either the PROfemale or PROmale instruction (Fig. 1C). The PROfemale instruction required participants to make a prosaccade toward the peripheral target following presentation of a female face, and an antisaccade away from the peripheral target following presentation of a male face. The PROmale instruction required the opposite. Use of the PROfemale and PROmale instruction was counterbalanced between participants. The face stimulus and target remained on screen together for 1000 ms after target appearance, and then the screen went black for 500 ms before the next trial began. The task consisted of 480 randomly interleaved pro- and antisaccade trials. Of the 480 trials, there was an equal distribution of pro- and antisaccade trials, as well as an equal distribution of the target appearing to the left or right of the face stimuli. Eighty trials were presented for each type of face stimuli, with 20 trials of each for each direction and sex. Breaks were offered every 32 trials to allow participants to re-adjust their position or for re-calibration of eye tracking.

2.3. Data analysis

Scripts written in MATLAB (Version R2014b; The MathWorks Inc., Natrick, MA, USA) were used to categorize micro- and macrosaccade behavior in each recorded trial. For our analysis, macrosaccades were defined as saccades with amplitudes greater than 2°, while microsaccades were defined as saccades with amplitudes less than 1.5° (Valsecchi & Turatto, 2009).

2.3.1. Macrosaccade behavior

Eye movements were detected on a trial-by-trial basis based on 3 sampling points of instantaneous speed. When sample points were 1.5 standard deviations from the speed of the background noise and the amplitude in the horizontal direction was greater than 2°, the eye movement was classified as a macrosaccade. Trials in which no saccades were made or the eye tracking signal was lost were excluded from this analysis. The measures of interest for this analysis included: anticipatory errors (saccades with latencies less than 90 ms relative to target appearance) for pro- and antisaccade trials, express saccades (saccades with latencies between 90 and 140 ms) for prosaccade trials, direction errors (saccades that did not follow the instructional cue for a given trial) for pro- and antisaccade trials, direction errors corrected (corrective saccades performed after direction errors) for antisaccade trials, and saccadic reaction time (SRT; time from target appearance to saccade initiation) for pro- and antisaccade trials. For each of these measures averages were taken for each participant, and were then used to compare averages between control, ADHD, and BD groups.

2.3.2. Microsaccade behavior

Microsaccade behavior was analyzed for the 800 ms period preceding target appearance (Fig. 1A) for each trial. Microsaccades were detected using a velocity-based algorithm developed by Engbert and colleagues (Engbert & Kliegl, 2003; Engbert & Mergenthaler, 2006). Eye positions were converted into 2D velocity space and microsaccades were classified when velocity components exceeded 6 standard deviations from the noise level for a given trial, and a minimum duration of 6 ms. Any trials in which a blink or saccade with an amplitude greater than 1.5° (classified as a fixation break) was made during the 800 ms window were excluded from this analysis. The measure of interest for this analysis was microsaccade rate. Following previous studies in which microsaccade rate was analyzed in bins with widths ranging from 20 to 100 ms (Hafed & Ignashchenkova, 2013; Valsecchi & Turatto, 2009), the microsaccade detection algorithm used here was applied to epoch bins of 50 ms which spanned the 600 ms of face stimuli fixation preceding correct pro- and antisaccade initiation. Individual microsaccade rate data was smoothed with a rectangular filter 50 ms wide. Microsaccade rate averages were taken for each participant, and were then used to compare averages between control, ADHD, and BD groups.

2.4. Statistical analysis

Preliminary analysis of the data revealed significant deviations from normality across macro- and microsaccade data for all participant groups. Nonparametric tests were therefore performed in SPSS 24 (SPSS IBM, New York, NY, USA) to investigate within- and between-group differences for our defined measures of interest. First, one-way ANOVAs and chi-square tests were conducted to investigate between-group differences in continuous and categorical demographic variables of age, sex, and level of education. Kruskal-Wallis tests were conducted to investigate between-group differences on prosaccade trials, antisaccade

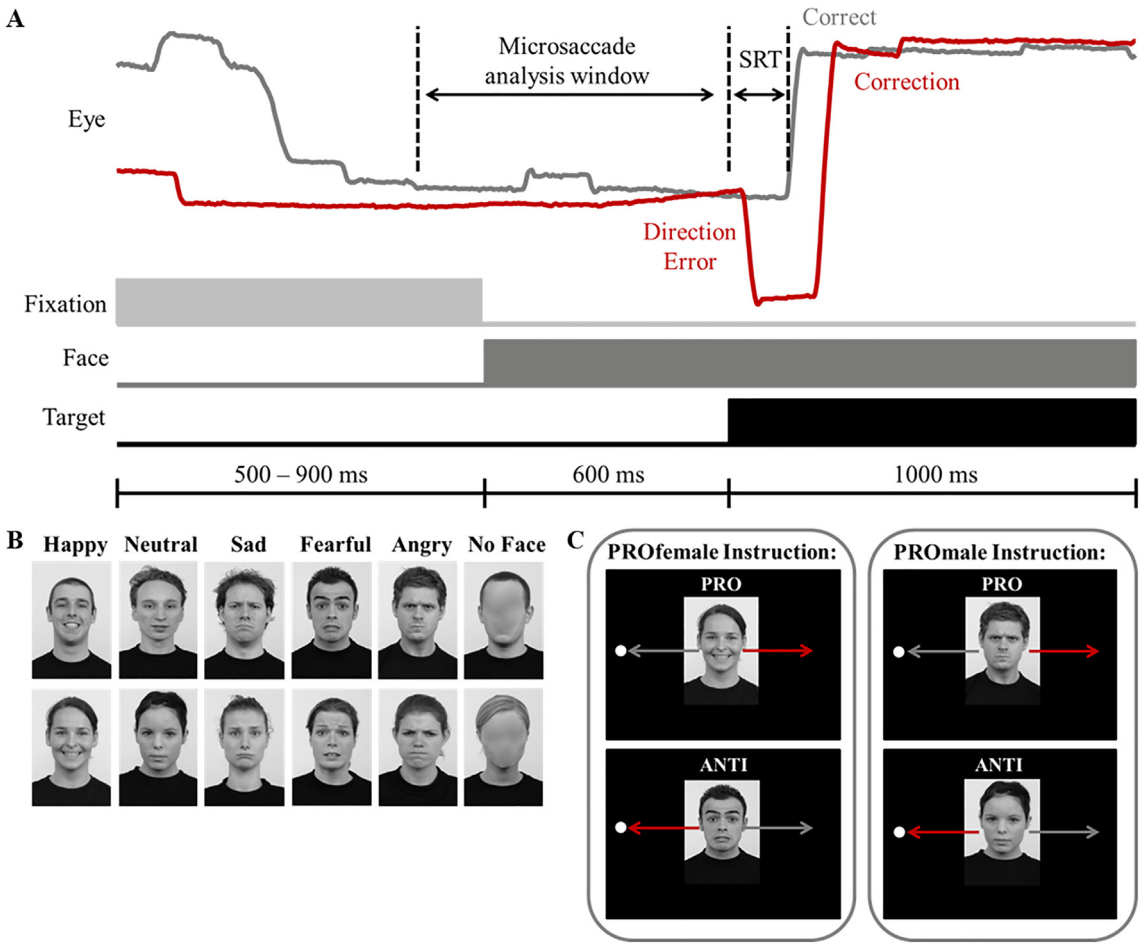

Fig. 1. A. Visual representation of the experimental paradigm over time. Each trial began with a central gray fixation cross (fixation), which remained on screen for 500–900 ms. The fixation cross was then replaced with a face stimulus (face) for 600 ms. After this point the peripheral target (target) appeared and remained on screen for 1000 ms. Eye represents a sample eye trace of a trial in which a correct saccade was made (gray) and a trial in which a direction error, followed by a correction was made (red). An 800 ms window was analyzed for microsaccade behavior and consisted of the last 200 ms of fixation and the 600 ms of face stimuli presentation before target appearance. Saccadic reaction time (SRT) is the time from target appearance to initiation of an eye movement. Direction errors are defined as saccades that did not follow the instructional cue for a given trial. B. Examples of face stimuli (happy, neutral, sad, fearful, angry, no face). C. Possible behavioral outcomes for PROfemale and PROmale instructions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

trials, and for each of the 6 types of face stimuli. Wilcoxon signed-rank tests and Friedman's ANOVAs were conducted to investigate within-group differences on pro- vs. antisaccade trials and across the 6 types of face stimuli, respectively. The Bonferroni correction was applied to adjust for multiple comparisons. Effect sizes are reported for all significant comparisons.

3. Results

3.1. Demographic differences

Performance on the pro/antisaccade task changes over the lifespan, with direction error percentage being the lowest and SRT being the shortest in participants in their early 20 s, and performance gradually declining with age (Alahyane, Brien, Coe, Stroman, & Munoz, 2014; Munoz, Broughton, Goldring, & Armstrong, 1998; Peltsch, Hemraj, Garcia, & Munoz, 2011). Education has also been shown to impact performance on the pro/antisaccade task (Evdokimidis et al., 2002), and furthermore women have been found to be faster and more accurate in processing emotional facial expressions than men (Forni-Santos & Osório, 2015; Hall, Hutton, & Morgan, 2010; Herlitz & Lovén, 2013). Therefore, we first investigated whether there were any group differences in age, level of education, or participant sex to ensure that these variables were not affecting task performance independently of participant group. A one-way ANOVA and chi-square tests revealed no significant differences between groups for age, level of education, distribution of participant sex, task instruction (PROfemale vs. PROmale) given, or the distribution of males and females given either task instruction. Given the considerable age range of participants recruited for this study, the macro- and microsaccade analyses described above were also conducted for participant groups when separated by sex and a median age split. The reduced sample size of these analyses resulted in nearly all between- and within-group analyses trending in the same direction as the complete analysis. However, significant results did not appear to be biased in any comparison by participant sex or age. These findings suggest that task performance was not significantly affected by ageing effects in the control group, or by potential interactions between aging and disease severity in the patient groups.

3.2. Macrosaccade behavior

3.2.1. Executive functioning

To assess executive functioning for the 3 participant groups, we first analyzed macrosaccade behavior on pro- and antisaccade trials, collapsed across all face stimuli types. The mean percentage of trials excluded due to the participant not initiating a saccade or the eye tracking

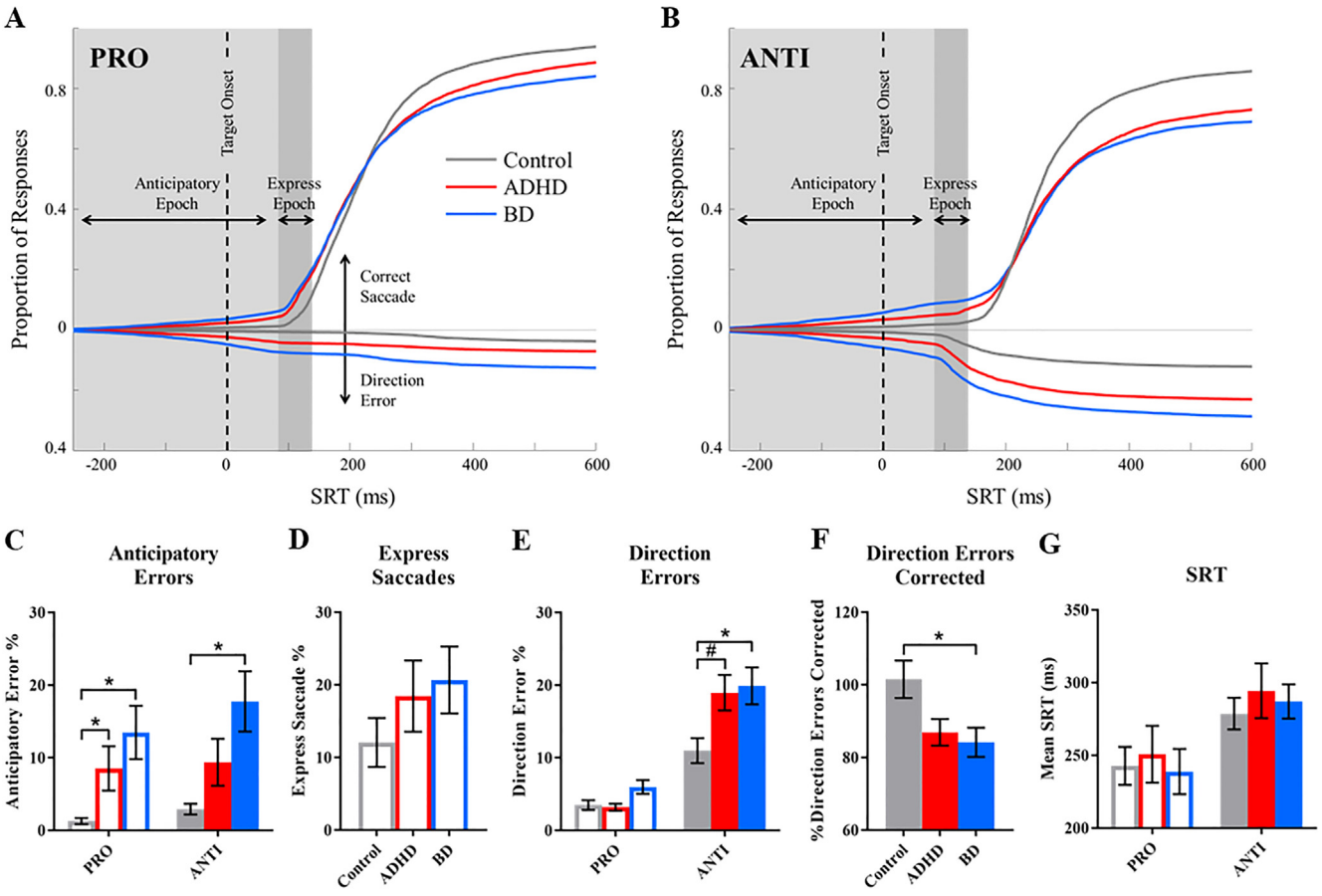

Fig. 2. (A, B) Cumulative distribution of responses collapsed across face stimuli types for all prosaccade (A) and antisaccade (B) trials for the 3 participant groups. Responses above the horizontal line represent correct saccades and those below represent direction errors. Light gray window represents the anticipatory epoch, occurring > 90 ms after target appearance. Saccades occurring during this epoch were classified as anticipatory errors. Dark gray window represents the express epoch, occurring 90–140 ms after target appearance. Saccades occurring during this epoch were classified as express saccades. Vertical shifts of the distributions represent changes in the proportion of direction errors made by each group, while horizontal shifts represent changes in the distribution of saccadic reaction times. (C – F) Percentage of trials in which anticipatory errors, express saccades, direction errors, and corrections of direction errors were made by each participant group. Empty bars represent prosaccade trials, filled bars represent antisaccade trials. (C) Percentage of anticipatory errors, occurring before 90 ms, for all pro- and antisaccade trials. (D) Percentage of express saccades, occurring between 90 and 140 ms, for all prosaccade trials. (E) Percentage of direction errors for all pro- and antisaccade trials. (F) Percentage of trials in which a corrective saccade was made following a direction error for all antisaccade trials. G. SRT for all pro- and antisaccade trials. # indicates .06 > p > .05, * indicates p < .05. Error bars represent standard error of the mean.

signal being lost (i.e. due to blinks) was higher in the BD group (mean = 9.87, SD = 12.89) as compared to the control (mean = 4.96, SD = 9.58) and ADHD group (mean = 5.06, SD = 5.56), however this difference was not statistically significant. Our within-group analysis investigated differences in direction errors and SRT, and as illustrated in Fig. 2A and B, trial type had a significant effect on performance across the 3 groups. Significantly more direction errors were made on antisaccade trials as compared to prosaccade trials for the control ($T = 226$, $p < .001$, $r = 0.59$), ADHD ($T = 209$, $p < .001$, $r = 0.61$), and BD ($T = 210$, $p < .001$, $r = 0.62$) groups. Similarly, SRT was significantly longer on antisaccade trials as compared to prosaccade trials for the control ($T = 226$, $p < .001$, $r = 0.59$), ADHD ($T = 203$, $p < .001$, $r = 0.58$), and BD ($T = 208$, $p < .001$, $r = 0.61$) groups. Our between-group analysis investigated differences in anticipatory errors, express saccades, direction errors, direction errors corrected, and SRT. The percentage of anticipatory errors made on prosaccade trials (Fig. 2C) was significantly different across groups ($H(2) = 16.38$, $p < .001$), with pairwise comparisons indicating that both the ADHD ($p = .007$, $r = -0.48$) and BD ($p < .001$, $r = -0.59$) group made significantly more errors than controls. The percentage of anticipatory errors made on antisaccade trials (Fig. 2C) was also significantly different across groups ($H(2) = 12.85$, $p = .002$), with the BD group making significantly more errors than controls ($p = .001$, $r = -0.56$). The percentage of express saccades made on prosaccade trials (Fig. 2D) followed a similar trend, however this difference was not significantly different across groups. The percentage of direction errors made on prosaccade trials (Fig. 2E) was significantly different across groups ($H(2) = 6.49$, $p = .039$), however pairwise comparisons did not yield any significance. The percentage of direction errors made on antisaccade trials (Fig. 2E) was significantly different across groups ($H(2) = 8.72$, $p = .013$), with the BD group making significantly more errors than controls ($p = .022$, $r = -0.42$). The difference between the ADHD and control group for antisaccade direction errors neared significance ($p = .052$, $r = -0.37$). The percentage of direction errors corrected on antisaccade trials (Fig. 2F) was also significantly different across groups ($H(2) = 7.19$, $p = .027$), with the BD group correcting significantly fewer direction errors than controls ($p = .045$, $r = 0.38$). There were no significant group differences in terms of pro- or antisaccade SRT (Fig. 2G).

3.2.2. *Emotion processing*

To assess emotion processing for the 3 participant groups, we analyzed macrosaccade behavior on pro- and antisaccade trials for each face stimulus type considered separately. Both our within- and between-group analysis investigated differences in direction errors and SRT. The only within-group analysis in which pairwise comparisons

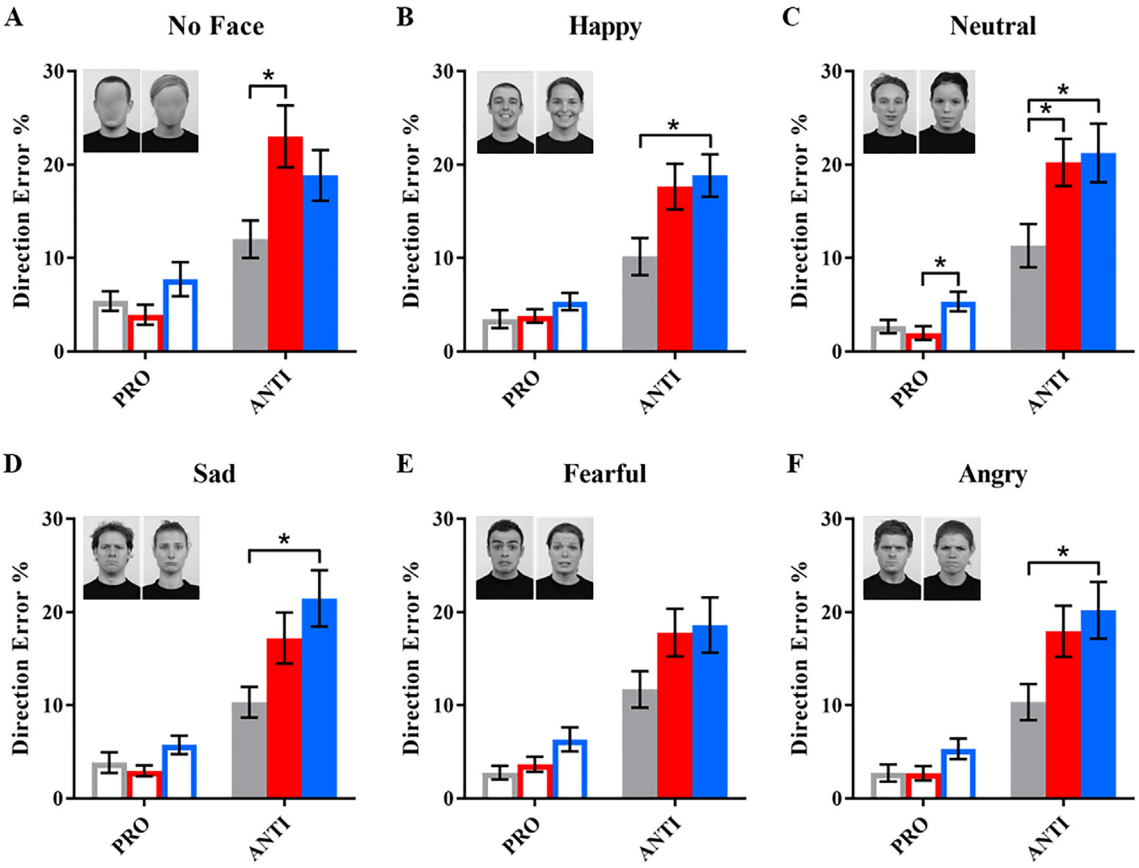

Fig. 3. Percentage of trials in which direction errors were made for no face (A), happy (B), neutral (C), sad (D), fearful (E), and angry (F) face stimuli presented on pro- and antisaccade trials for each participant group. * indicates $p < .05$. Error bars represent standard error of the mean.

yielded a significant result was for antisaccade SRT in the ADHD group ($X_F^2(5) = 12.17$, $p = .033$), with longer SRT for neutral stimuli as compared to happy stimuli ($p = .046$, $r = -0.47$). In terms of the between-group analysis, direction errors made on prosaccade trials were significantly different across groups for neutral stimuli, with the BD group making significantly more errors than the ADHD group (Fig. 3C; $p = .013$, $r = -0.45$). Direction errors made on antisaccade trials were significantly different across groups for all face stimuli, with the exception of fearful stimuli. Pairwise comparisons indicated that the ADHD group made significantly more errors than controls on no face (Fig. 3A; $p = .022$, $r = -0.42$), and neutral (Fig. 3C; $p = .041$, $r = -0.39$) stimuli, while the BD group made significantly more errors than controls on happy (Fig. 3B; $p = .015$, $r = -0.44$), neutral (Fig. 3C; $p = .043$, $r = -0.38$), sad (Fig. 3D; $p = .007$, $r = -0.48$), and angry (Fig. 3F; $p = .024$, $r = -0.42$) stimuli. There were no significant group differences in terms of pro- or antisaccade SRT for any of the face stimuli types.

3.3. Microsaccade behavior

3.3.1. Executive functioning

To further assess executive functioning, we analyzed microsaccade rates during fixation of face stimuli preceding correct pro- and antisaccade initiation, collapsed across all face stimuli types. We first investigated whether there were any between-group differences in the percentage of trials excluded due to fixation breaks made during the microsaccade analysis window. Our analysis revealed that the percentage of trials excluded preceding both pro- ($H(2) = 9.82$, $p = .007$) and antisaccade ($H(2) = 8.62$, $p = .013$) initiation was significantly different across groups (Fig. 4A). Pairwise comparisons indicated that preceding prosaccade trials, both the ADHD ($p = .029$, $r = -0.40$) and BD ($p = .015$, $r = -0.44$) group made significantly more fixation breaks than controls, and that preceding antisaccade trials, the BD group made significantly more fixation breaks than controls ($p = .018$, $r = -0.43$).

As illustrated in Fig. 4B-F, the time course of microsaccade rate change following face stimuli appearance in the 3 groups is consistent with the characteristic suppression, rebound, and suppression response that has been described in the literature (Engbert & Kliegl, 2003; Rolfs et al., 2008). Here, initial microsaccade suppression occurred at 100–150 ms following face stimuli appearance, the peak of the rebound occurred at 250–300 ms following face stimuli appearance, and the secondary suppression occurred at 550–600 ms following face stimuli appearance, close to the time of target appearance. Our within-group analysis revealed that the control group had significantly lower microsaccade rates preceding anti- vs. prosaccade initiation from 300 to 350 ms after face stimuli appearance (Fig. 4B; $T = 51$, $p = .025$, $r = -0.35$). Interestingly, the opposite trend was true for the ADHD group (Fig. 4C) in that they had significantly lower microsaccade rates preceding pro- vs. antisaccade initiation from 150 to 200 ms ($T = 162$, $p = .033$, $r = 0.34$) and 200–250 ms ($T = 168$, $p = .019$, $r = 0.37$) after face stimuli appearance. The BD group (Fig. 4D) did not exhibit any significant differences in microsaccade rate preceding pro- vs. antisaccade initiation. Although the BD group exhibited an overall suppression of microsaccade rate as compared to the control and ADHD group, inter-subject variability for all 3 groups was high, and our between-group analysis did not reveal any significant differences in microsaccade rates preceding pro- (Fig. 4E) or antisaccade trials (Fig. 4F).

3.3.2. Emotion processing

We also analyzed microsaccade rates during fixation of face stimuli preceding correct pro- and antisaccade initiation for each face stimulus

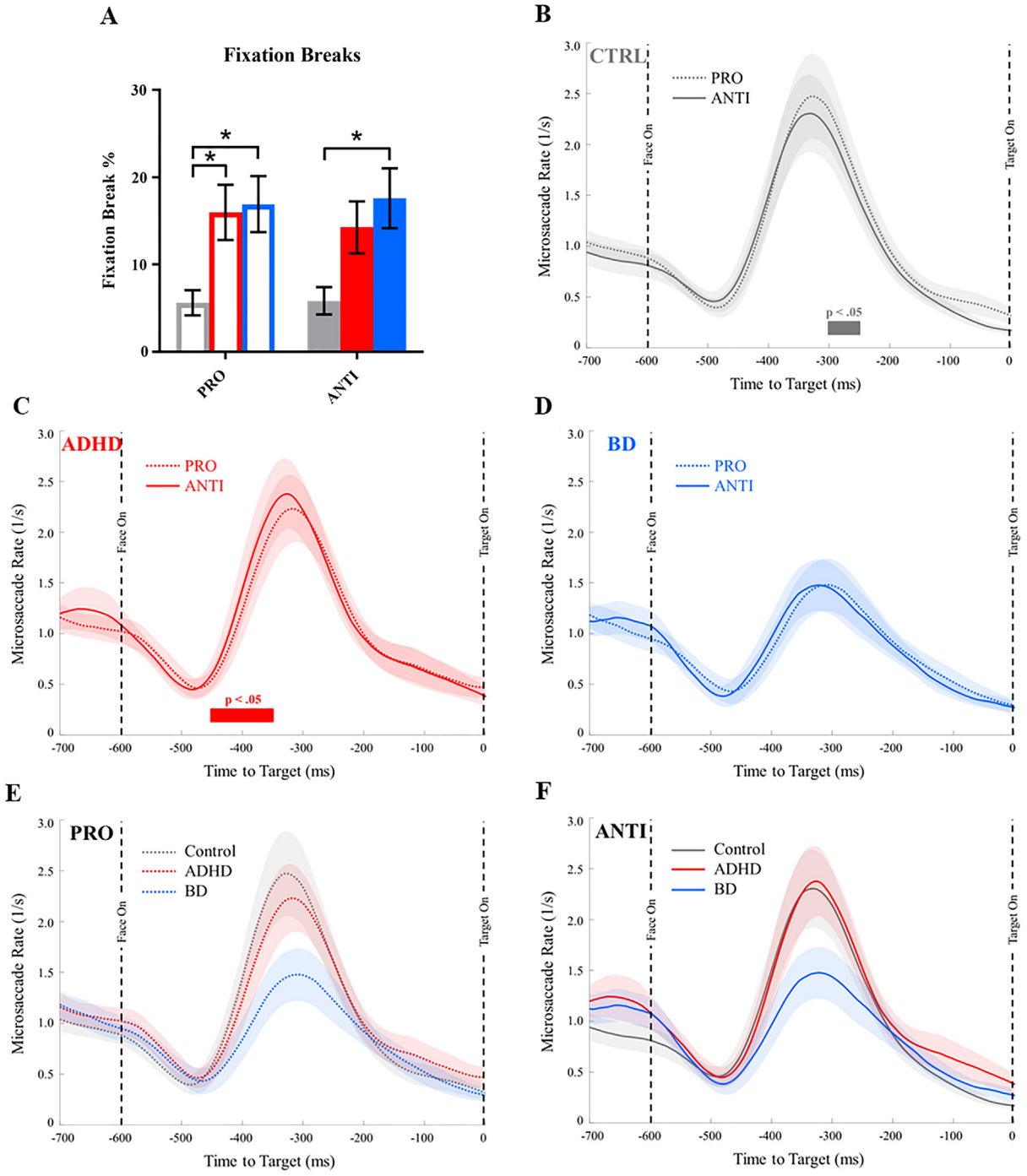

Fig. 4. A. Percentage of trials excluded from microsaccade analysis for each participant group due to fixation breaks. * indicates $p < .05$. Error bars represent standard error of the mean. (B – D). Time course of microsaccade rate change during face stimuli fixation for all correct pro- and antisaccade trials collapsed across all face stimuli types for the control (B), ADHD (C), and BD (D) group. Horizontal bars represent time windows during which microsaccade rates preceding pro- and antisaccade initiation differed significantly from one another. (E and F) Time course of microsaccade rate change during face stimuli fixation for all correct prosaccade (E) and antisaccade (F) trials for the 3 participant groups. Shaded regions on graphs represent standard error of the mean.

type considered separately. For this analysis we report significant differences in microsaccade rates which occurred at the epoch centered at the peak of the microsaccade rebound, 250–300 ms after face stimuli appearance. This rebound peak has been shown to reflect shifts in covert attention (Engbert & Kliegl, 2003), including those driven by the presentation of emotional stimuli (Kashihara et al., 2014). Our within-group analysis revealed that microsaccade rates preceding both pro- and antisaccade initiation were significantly different across face stimulus type for each of the 3 groups. For the control group, microsaccade rates were significantly lower on no face stimuli as compared to happy, neutral, sad, and fearful stimuli (Fig. 5A; all p's $< .05$, all r's > -0.50) preceding prosaccade initiation, and significantly lower on no face stimuli as compared to neutral, sad, fearful, and angry stimuli (Fig. 5B; all p's < 0.05 , all r's > -0.50) preceding antisaccade initiation. For the ADHD group, microsaccade rates were significantly lower on no face stimuli as compared to all other face stimuli (Fig. 5A; all p's < 0.05, all r's > -0.50) preceding prosaccade initiation, and significantly lower on no face stimuli as compared to sad

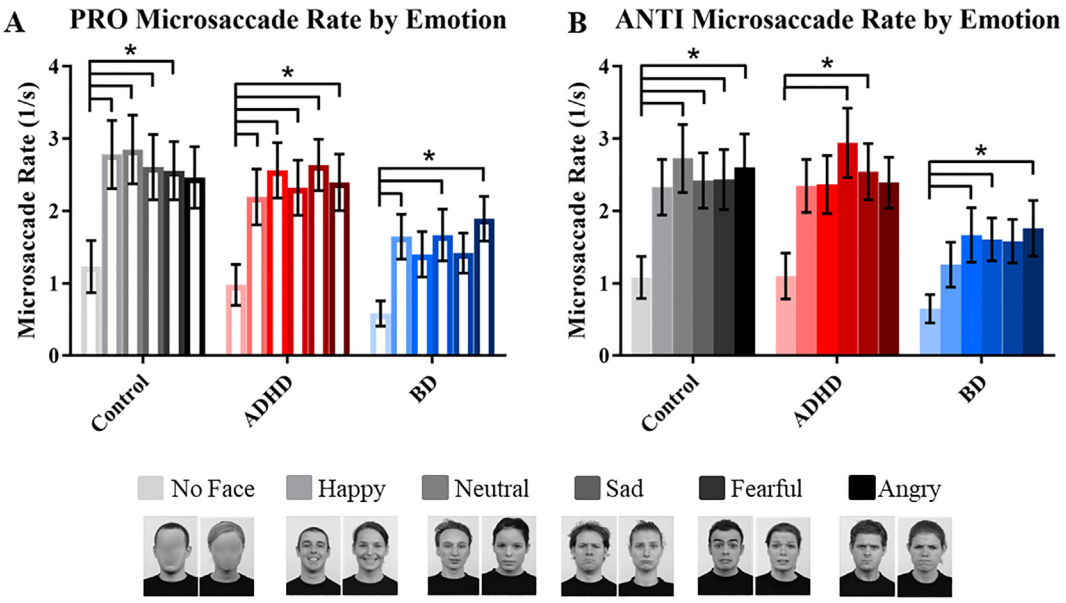

Fig. 5. (A, B) Microsaccade rates centered at the peak of the microsaccade rebound (250–300 ms after face stimuli appearance) separated by face stimuli type for all correct prosaccade (A) and antisaccade (B) trials for the 3 participant groups. * indicates $p < .05$. Error bars represent standard error of the mean.

($p < .001$, $r = -0.67$), and fearful ($p = .035$, $r = -0.48$) stimuli (Fig. 5B) preceding antisaccade initiation. For the BD group, microsaccade rates were significantly lower on no face stimuli as compared to happy, sad, and angry stimuli (Fig. 5A; all p's $< .05$, all r's > -0.50) preceding prosaccade initiation, and significantly lower on no face stimuli as compared to neutral, sad, and angry stimuli (Fig. 5B; all p's $< .05$, all r's > -0.40) preceding antisaccade initiation. The only between-group analyses in which pairwise comparisons yielded a significant result were for neutral stimuli preceding prosaccade trials ($H(2) = 7.57$, $p = .023$), with the control group having a significantly higher microsaccade rate than the BD group ($p = .044$, $r = 0.38$), and for fearful stimuli preceding prosaccade trials ($H(2) = 6.94$, $p = .031$), with the ADHD group having a significantly higher microsaccade rate than the BD group ($p = .046$, $r = 0.38$).

4. Discussion

The goal of this study was to characterize executive functioning and emotion processing in adult ADHD and BD through investigation of both macro- and microsaccade behavior on an emotional pro/antisaccade task. Our hypothesis that executive functioning would differentiate patient groups from controls was supported: both ADHD and BD participants made more direction and anticipatory errors than controls. Furthermore, while the control group exhibited a lower microsaccade rate preceding the initiation of correct anti- vs. prosaccades, this important task-related modulation was absent in both patient groups. Our second hypothesis - that emotion processing would differentiate patient groups from one another - was not supported, however, as compared to controls, BD participants exhibited a greater overall impairment in emotion processing than ADHD participants. Taken together, these findings demonstrate that response inhibition deficits are central to both ADHD and BD, and that they are further impaired in BD individuals when simultaneously engaged in emotion processing.

4.1. Executive functioning

We assessed executive functioning by analyzing macro- and microsaccade behavior on pro- vs. antisaccade trials. Similar to previous findings (Feifel et al., 2004; Gooding & Tallent, 2001; Hakvoort Schwerdtfeger et al., 2013; Harris et al., 2009; Malsert et al., 2013; Martin et al., 2007; Munoz et al., 2003; Nigg et al., 2002; Soncin et al., 2016), failure of inhibitory control was evident in both patient groups, with ADHD and BD participants making significantly more direction errors than controls (Fig. 2E). Both patient groups also made significantly more anticipatory errors than controls (Fig. 2C). Given that anticipatory errors occur before adequate time has passed to allow for processing of the peripheral target, these types of errors reflect a failure to inhibit prepotent motor responses. Elevated anticipatory errors have been reported previously in ADHD (Carr, Nigg, & Henderson, 2006; Feifel et al., 2004; Nigg et al., 2002), and have been proposed as an additional index of deficient attentional and inhibitory control mediated by dysfunctional dlPFC circuitry (Feifel et al., 2004). Saccade paradigms have been less frequently employed in BD populations (Bittencourt et al., 2013), therefore our findings of elevated anticipatory errors in this group may lend further support for dysfunctional dlPFC circuitry in BD. Given that impulsivity is a trait shared by both disorders, elevated anticipatory errors may provide a proxy for this behavioral deficit in both ADHD and BD. In this paradigm BD participants also corrected significantly fewer direction errors than controls (Fig. 2F). This interesting and somewhat novel finding may reflect deficits in a number of processes which have been previously characterized in BD, including sustained attention (Sepede et al., 2012; Strakowski, Adler, Holland, Mills, & DelBello, 2004) and working memory (Adler, Holland, Schmithorst, Tuchfarber, & Strakowski, 2004; Volkert et al., 2016). Compared to the ADHD and control group, BD participants also made a higher proportion of express saccades and contributed less viable trials (possibly due to not initiating a saccade). These findings may suggest that the emotional stimuli presented in this task negatively affected inhibitory and impulsive control in BD participants more so than in ADHD participants (Green, Cahill, & Malhi, 2007; Hummer et al., 2013).

We additionally quantified microsaccade rates preceding correct pro- and antisaccade initiation. Previous research in healthy controls has demonstrated lower microsaccade rates prior to the initiation of correct anti- vs. prosaccades, which is thought to reflect preparation by the basal ganglia to suppress erroneous prosaccades that are automatically programmed toward the peripheral target (Watanabe et al., 2013). Additionally, while ADHD cohorts have been found to make more intrusive saccades when instructed to maintain central fixation as compared to controls (Fried et al., 2014; Gould, Bastain, Israel, Hommer, & Castellanos, 2001; Munoz et al., 2003), the same behavior did not distinguish BD cohorts from controls (Gooding, Grabowski, &

Hendershot, 2000). Here, both ADHD and BD participants made significantly more fixation breaks than controls during the fixation epoch, and while control participants exhibited a significantly lower microsaccade rate preceding anti- vs. prosaccade initiation, this task-related modulation was absent in both patient groups. Given that abnormal functioning of the basal ganglia has been implied in the pathology of both ADHD (Giedd, Blumenthal, Molloy, & Castellanos, 2001; Hart et al., 2013; Nigg & Casey, 2005) and BD (Chen, Suckling, Lennox, Ooi, & Bullmore, 2011; Teng et al., 2013, 2014), the elevated rate of fixation breaks and lack of microsaccade rate modulation reported here may reflect preparatory and/or attentive deficits in these two disorders. Consistent with this finding, Hakvoort Schwerdtfeger et al. (2013) found that ADHD individuals perform poorly on an interleaved pro/antisaccade task due to deficits in saccade preparation rather than deficits in saccade execution, with FEF, SEF, and PEF being less activated in ADHD individuals as compared to controls during the period preceding antisaccade initiation.

4.2. Emotion processing

Emotion processing was assessed by analyzing macro- and microsaccade behavior for each face stimulus type considered separately. The ADHD group made significantly more direction errors than controls on antisaccade trials presenting no face and neutral stimuli, while the BD group made significantly more direction errors than controls on antisaccade trials presenting all emotional face stimuli except fearful stimuli. That BD participants were differentiated from controls on trials presenting 4 of the 5 emotional stimuli used in our paradigm is consistent with the range of literature describing attentional biases and processing deficits across positively, negatively, and neutrally valenced stimuli in BD (Brotman et al., 2008; Degabriele et al., 2011; Malhi & Lagopoulos, 2007). The finding that BD participants did not differ from controls on trials presenting fearful stimuli was, however, unexpected. Previous studies have reported that individuals with BD are slower to identify fearful faces (Malhi & Lagopoulos, 2007), correctly identify fear less often than other emotions (De Brito Ferreira Fernandes et al., 2016), and show abnormal activation of the amygdala and hippocampus when attending to or discriminating fearful faces (Brotman et al., 2014; Malhi & Lagopoulos, 2007). The discrepancy between our findings and the findings of previous studies may therefore have resulted from the use of different paradigms and sets of stimuli. Alternatively, it is possible that combining the task paradigm used here with neuroimaging may reveal functional activation changes in regions such as the amygdala and hippocampus in BD participants which are not mirrored in behavioral results.

In our previous paradigm, Soncin et al. (2016) also found that neutral face stimuli differentiated both patient groups from controls. Neutral stimuli have been shown to elicit emotional hyper-reactivity in BD (Lemaire, El-Hage, & Frangou, 2015; M'Bailara et al., 2009; Stratta, Tempesta, Bonanni, de Cataldo, & Rossi, 2014), and amygdala hyperactivation in both ADHD and BD (Brotman et al., 2010, 2014). It has been suggested that neutral faces may not, in fact, be evaluated as emotionally neutral but rather similarly to negatively valenced faces (Lee, Kang, Park, Kim, & An, 2008). This perception of neutral/ambiguous faces as being negatively valenced has been reported in a number of psychiatric disorders (Lemaire et al., 2015; Mitchell, Dickens, & Picchioni, 2014), and may provide a unique marker of a negative affective bias to cognitive control in psychiatric illness. Indeed, while both patient groups made significantly more direction errors on trials presenting neutral stimuli as compared to controls, our within-group analysis revealed that the ADHD group also had significantly longer SRT on antisaccade trials presenting neutral stimuli as compared to happy stimuli, suggesting a potential speed-accuracy compensation to this stimulus type in the ADHD group which was absent in the BD group. In contrast to the findings of Soncin et al. (2016), BD participants were not slower on trials of neutrally and negatively valenced faces. Here, the high proportion of express saccades made by the BD group - possibly reflecting a negative effect of emotion processing over inhibitory control - likely contributed to the shorter SRTs than what was observed in our previous study. In this paradigm the no face stimulus was used as a control to emotional stimuli, however, ADHD participants made the most direction errors on trials presenting this type of stimulus. If this behavior was the result of participants being unable to discriminate male vs. female sex from this stimulus, we would expect direction error percentage to be similarly high for the BD and control groups when comparing performance on trials presenting the no face stimulus to trials presenting emotional stimuli. This, however, was not the case. It is therefore possible that the saliency of the no face stimuli negatively affected attentional and inhibitory control in the ADHD group more so than in the BD or control group. Future work validating the use of such a stimulus as a control for emotion processing is needed.

Analysis of microsaccade rates during the presentation of different face stimuli types revealed only subtle differences between the types of emotional face stimuli, but a robust differentiation between the no face and emotional stimuli for all 3 groups. Microsaccade behavior has been shown to be a measure of visual attention driven by both saliency (Wang, Blohm, Huang, Boehnke, & Munoz, 2017), and emotion processing (Kashihara et al., 2014), both of which may have been reflected in the higher microsaccade rates for the emotional vs. no face stimuli observed here. Further work is required to clarify how various aspects of facial and emotion processing may be reflected in microsaccade rate, and whether it can provide a means of probing abnormal emotion processing in psychiatric disorders. Although we were unable to differentiate ADHD and BD groups from one another on the basis of emotion processing, comparison of each group to controls suggests that BD individuals experience a more global deficit in emotion processing, possibly exaggerated by the cognitive demands of this task, whereas ADHD individuals may be specifically affected by neutrally/ambiguously valenced stimuli.

4.3. Anatomical substrate of task performance

Cognitive control and emotion processing systems share complex and reciprocal interactions in the brain which are necessary for goal-directed behavior (Kanske, 2012; Mueller, 2011; Uekermann, Abdel-Hamid, Lehmkämper, Vollmoeller, & Daum, 2008). Saccade tasks provide a sensitive means of engaging both of these systems: regions of the oculomotor circuit, such as the dlPFC, FEF, SEF, PEF, basal ganglia, and thalamus are also involved in cognitive control (Bari & Robbins, 2013; Rubia et al., 2006; Sweeney, Luna, Keedy, McDowell, & Clementz, 2007), and have reciprocal connections with subcortical emotion circuits, which have been suggested to influence the preparation and execution of saccades when emotional stimuli are incorporated into the paradigm (Kissler & Keil, 2008; West, Al-Aidroos, Susskind, & Pratt, 2011). The paradigm used here therefore provides a novel way to probe the integrity of both executive functioning and emotion processing in ADHD and BD, two disorders which have been previously characterized by dysregulation of the dlPFC, amygdala, and basal ganglia (Blumberg & Leung, 2003; Giedd et al., 2001; Hakvoort Schwerdtfeger et al., 2013; Hart et al., 2013; Phillips & Swartz, 2014; Pompei, Dima, Rubia, Kumari, & Frangou, 2011; Schulz et al., 2014; Strakowski et al., 2005). As discussed above, our assessment of executive functioning on this task revealed impairments in both patient groups, which are likely mediated by dysfunctional fronto-striatal circuitry involving the dlPFC and basal ganglia. Previous studies have demonstrated a reciprocal relationship between cognitive control and emotion processing, whereby emotion processing is critically dependent on the availability of cognitive processing resources, and vice-versa (Cohen et al., 2015; Jasinska et al., 2012; Kalanthroff et al., 2013; Schupp et al., 2007). There is growing support for the notion of an emotional bias in cognitive control in psychiatric illness, potentially mediated by dysregulated frontal-

subcortical circuits connecting the dlPFC, ACC, and OFC with the striatum and thalamus (Bonelli & Cummings, 2007). This pattern of abnormal emotion-cognition interactions has been proposed to play an important role in ADHD (Shaw, Stringaris, Nigg, & Leibenluft, 2014) and BD (Green et al., 2007), and is supported by neuroimaging studies which have investigated the effects of emotional stimuli on cognitive control in adults with both disorders. When required to inhibit emotional information (in paradigms such as the emotional go/no-go task and affective Stroop task), ADHD participants have been found to show reduced connectivity between right dlPFC and subgenual cingulate cortex, inferior frontal gyrus, and putamen (Schulz et al., 2014), and BD cohorts have been reported to exhibit abnormal activation of prefrontal cortex, orbitofrontal cortex, insula, and amygdala (Favre, Polosan, Pichat, Bougerol, & Baciu, 2015; Hummer et al., 2013). Based on these findings, we would expect that in our task, antisaccade trials presenting emotional face stimuli would elicit emotion processing which may utilize an excess of cognitive processing resources in both patient groups, and it is these cognitive processing resources which would have otherwise contributed to successful task performance in healthy controls. In BD participants this was reflected in performance on antisaccade trials presenting stimuli of all valences, while in ADHD participants this was reflected most strongly in performance on antisaccade trials presenting neutrally valenced stimuli.

That the BD group demonstrated an overall greater level of impairment on this task suggests a different pattern of neural activation in these individuals when required to recruit cognitive control and emotion processing systems simultaneously. The ACC and OFC are two structures which are extensively connected to other cortical and subcortical regions of the brain (Phillips, Drevets, Rauch, & Lane, 2003; Phillips, Ladouceur, & Drevets, 2008), play important roles in the regulation of both cognitive and emotional processes (Mohanty et al., 2007; Rolls, 2004), and may have contributed to the performance of BD participants on the task used here. Indeed, hypoactivation of both the ACC and OFC (Delvecchio, Sugranyes, & Frangou, 2012; Green et al., 2007; Phillips et al., 2008), as well as abnormal connectivity between these two structures and the amygdala (Townsend & Altshuler, 2012; Versace et al., 2010) has been suggested to contribute to the high degree of emotional dysregulation in BD. Based on the findings presented here, we propose that fronto-striatal circuitry mediates response inhibition deficits in both ADHD and BD, and that dysregulated limbic system circuitry involving the amygdala, ACC, and OFC may exacerbate this deficit in BD when simultaneously engaged in emotion processing. However, neuroimaging studies which directly compare ADHD and BD during tasks of cognitive and emotion processing are needed to clarify the similarities or differences in neural substrates which are recruited in these two disorders.

4.4. Limitations and future directions

The task paradigm used here allowed us to investigate emotion processing across a range of emotional stimuli, however, future work may benefit from the simplification of conditions to allow for greater statistical power per comparison. This study is limited by the relatively small sample sizes used in combination with the large number of within- and between-group comparisons investigated. A second limitation was in comparing one patient group off-medication (ADHD group) to one that remained on-medication (BD group). Lithium (Wingo, Wingo, Harvey, & Baldessarini, 2009) and antipsychotics (Hughes, Lynch, Rhodes, Ervine, & Yates, 1999; Morrens et al., 2007; Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008) have been shown to affect psychomotor speed and cognition, however a number of studies have reported that medication did not affect saccade task performance in BD individuals (Harris et al., 2009; Keedy et al., 2014; Thakkar, Schall, Logan, & Park, 2015). Furthermore, having BD individuals continue their medication increased the likelihood that they remained in a euthymic mood state at the time of testing. This is an important consideration given that emotion processing deficits in BD have been shown to vary based on mood state (Hummer et al., 2013; Phillips et al., 2008).

5. Conclusions

Our ability to distinguish the symptomology of ADHD and BD, as well as our understanding of the mechanisms underlying these two disorders, is limited by a lack of behavioral biomarkers that support clinical assessment and diagnosis. The findings presented here support the notion that response inhibition, mediated by fronto-striatal circuitry, is a central deficit in both ADHD and BD, and that it is exacerbated by more global emotion processing deficits, presumably mediated by dysregulated limbic system circuitry involving the amygdala, ACC and OFC, in BD. We extend upon these findings by suggesting that microsaccade rate may serve as a valuable marker of preparatory and attentive deficits in these two disorders. Neuroimaging studies investigating cognitive and emotion processing in ADHD and BD are needed in order to develop a better understanding of the neural mechanisms underlying the behaviors described here, and will be a critical step forward in advancing the development of behavioral biomarkers in these two disorders.

Conflicts of interest

The authors report no conflicts of interest.

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