

# Evidence that eye-movement profiles do not explain slow binocular rivalry rate in bipolar disorder: support for a perceptual endophenotype

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**Objectives:** Presenting conflicting images simultaneously, one to each eye, produces perceptual alternations known as binocular rivalry (BR). Slow BR rate has been proposed as an endophenotype for bipolar disorder (BD) for use in large-scale genome-wide association studies. However, the trait could conceivably reflect eye movement (EM) dysfunction in BD rather than anomalous perceptual processing per se. To address this question, we examined the relationship between EM profiles and BR rate for various stimulus types in BD and healthy subjects. We also examined differences in EM profiles between these groups.

**Methods:** Employing a repeated-measures within-subjects design, 20 BD outpatients and 20 age- and sex-matched healthy controls completed EM tasks and separate BR tasks involving a range of stimuli with different drift speeds. The association between each EM measure and BR rate was examined with correlational analyses for all stimulus conditions in both groups. Between-group comparisons were performed to determine any differences in those EM measures. Corresponding Bayesian analyses were also conducted.

**Results:** There were no EM measures that showed a significant relationship with BR rate in either the BD group or the healthy group ( $P \geq 7.87 \times 10^{-3}$ ), where those EM measures were also significantly different *between* the BD and healthy groups ( $P \geq 1.32 \times 10^{-2}$ ). These findings were verified with Bayes factors.

**Conclusions:** The results provide evidence that EM profiles do not explain the slow BR endophenotype for BD, thus indicating that the trait reflects anomalous perceptual processing per se. This perceptual trait can be employed in clinical, genetic, mechanistic and pathophysiological studies.

## KEYWORDS

Bayes factors, binocular rivalry, bipolar disorder, endophenotype, individual variation, perceptual alternation rate, saccadic eye movements

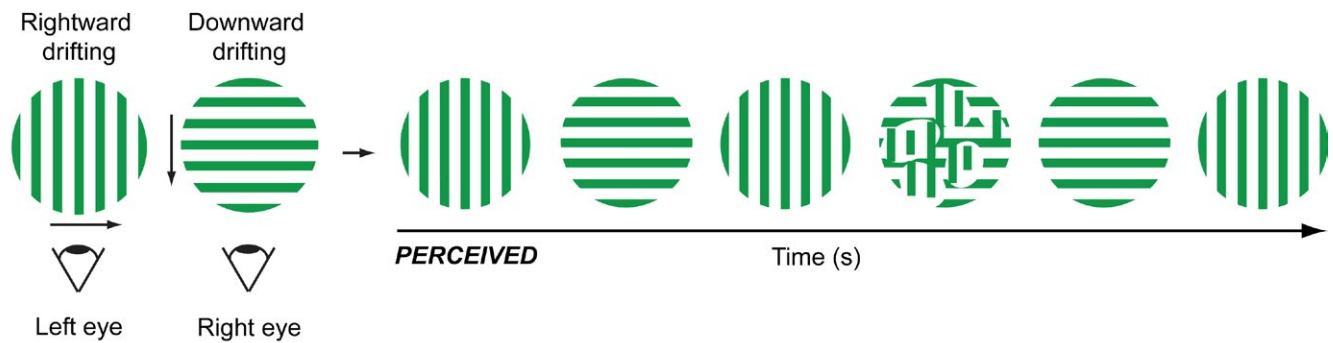
## 1 | INTRODUCTION

Binocular rivalry (BR) is an intriguing visual phenomenon in which conflicting images presented to each eye are perceived in alternation

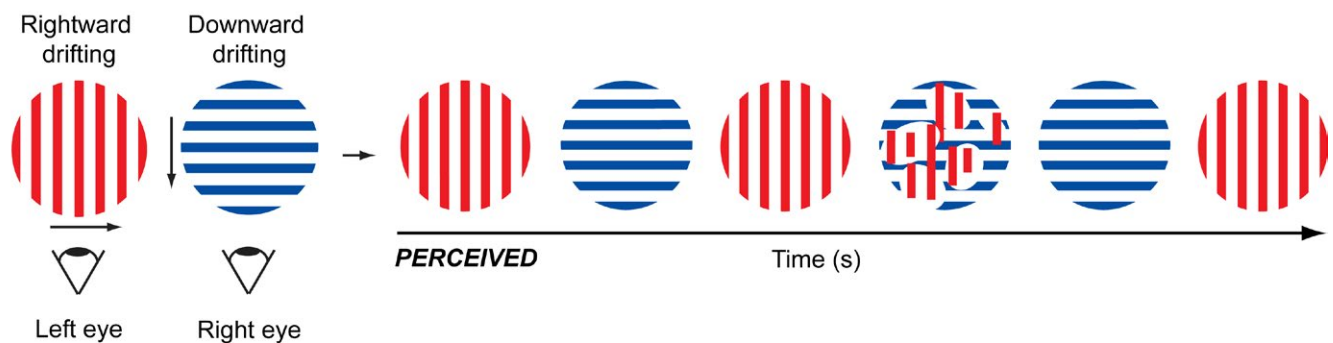
rather than being superimposed. For example, simultaneously presenting a vertical grating to one eye, and a horizontal grating to the other eye, induces perception of the vertical grating for a few seconds, followed by perception of the horizontal grating for a few seconds, and so on (Figure 1). A great deal is known about the psychophysics and neurophysiology of BR but underlying neural mechanisms are not yet

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## (A) PRESENTED STIMULI



## (B) PRESENTED STIMULI



**FIGURE 1** Binocular rivalry with (A) green gratings and (B) red/blue gratings. Presenting dissimilar images—such as rightward-drifting vertical gratings and downward-drifting horizontal gratings—simultaneously, one to each eye, causes each image to stochastically alternate in perception. Mixed percepts (i.e., portions of both eyes' presented images are simultaneously visible) occur occasionally during the transition between perception of presented images. Arrows in presented stimuli denote the direction of grating drift. s, seconds [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

fully understood.<sup>1-3</sup> However, it has long been known that the rate of perceptual alternation or *BR rate* varies widely between individuals but is relatively stable within individuals.<sup>4-13</sup>

Over recent decades, interest in examining BR in psychiatric disorders followed reports that BR rate is slow in bipolar I disorder (BD) but not in schizophrenia (SCZ) or major depressive disorder (MDD).<sup>14,15</sup> For example, in BD, perceptual switches occur on average every 3-4 seconds (with some periods up to 7-10 seconds), compared with every 1-2 seconds in healthy individuals. The finding of a slow BR rate in BD has since been independently replicated<sup>16-18</sup> and, notably, the historical literature reported corresponding evidence for switch rate of ambiguous figures (a different form of perceptual rivalry).<sup>19,20</sup> Slow BR rate in BD also appears to be unaffected by either clinical state or medication<sup>14,17</sup> (but see Jia et al.,<sup>21</sup> who report some effect of depressive state on BR rate; see also Zhu et al.<sup>18</sup>). These findings—together with the demonstration that an individual's BR rate is approximately 50% genetically determined<sup>9,22</sup>—supported the proposal that slow BR is an endophenotype for BD, suitable for use in large-scale genome-wide association studies (GWAS).<sup>11,23-25</sup> Stimulus parameters for such studies are being optimized (P. C. F. Law, S. M. Miller, & T. T. Ngo, in preparation), and because thousands to tens of thousands of subjects are required for GWAS, an online platform of BR testing is being developed.<sup>23</sup> However, aspects of the slow BR trait require further investigation.<sup>25</sup>

One such aspect is whether slow BR in BD might reflect eye movement (EM) dysfunction in the disorder. This possibility is based on widely reported findings of EM deficits in psychiatric populations, especially in SCZ.<sup>26-29</sup> However, in BD (which has a shared genetic basis with SCZ),<sup>30</sup> EMs have not been extensively investigated and existing studies have reported inconsistent results.<sup>26,27,31</sup> For example, BD has been associated with impaired maintenance pursuit gain,<sup>32-35</sup> impaired predictive (primary) saccade gain,<sup>36</sup> and increased antisaccade error,<sup>37-40</sup> but these findings have not been replicated by other studies.<sup>41-43</sup> As such, it is possible that slow BR in BD may arise simply due to anomalous EMs associated with the disorder, rather than perceptual processing abnormalities per se.

The relationship between EMs and BR is complex. Early work found that BR still occurs with afterimages (i.e., when stimuli are stabilized on the retina), and thus saccadic EMs are not required for BR.<sup>44-46</sup> Despite this observation, the rate of BR is faster with real images than afterimages, suggesting saccadic EMs may indeed influence BR rate.<sup>44,45,47</sup> In later studies of EMs recorded during BR viewing, saccadic EMs that induced retinal image shifts were shown to be associated with perceptual switches.<sup>48,49</sup> In a recent study by Hancock et al.,<sup>50</sup> an association was also found between a healthy individual's frequency of saccadic EMs (during a free-viewing task) and their BR rate when these measures were recorded in separate experimental conditions. However, these findings were not replicated by Law

et al.,<sup>51</sup> who showed no relationship between BR rate and healthy individuals' saccadic EM frequency using a similar experimental protocol and double the sample size. Law et al.'s study<sup>51</sup> also extended the work of Hancock et al.<sup>50</sup> by assessing additional EM measures that had been used to show performance deficits in psychiatric groups (especially in BD and SCZ<sup>26–29,32,33,36–40,42,43,52</sup>), and found no relationship between these EM measures and BR rate.

The study by Law et al.<sup>51</sup> provided indirect evidence that EMs do not account for the slow BR endophenotype; however, the authors pointed out that direct investigation of EMs and BR rate in a BD cohort was required to support this conclusion. The current study therefore aimed to examine EM profiles and BR rate in a group of BD subjects and age- and sex-matched healthy controls, with EM and BR measures recorded in separate experimental conditions. The study protocol also enabled assessment of a secondary aim, i.e., group differences in EM profiles between BD and healthy subjects—an issue that has not been studied extensively to date.

## 2 | PATIENTS AND METHODS

### 2.1 | Sample and clinical assessment

Twenty naïve clinically stable outpatients with BD (12 male; mean age = mean ± standard deviation (SD) 41.6 ± 13.4 years) and 20 age- and sex-matched healthy controls (mean age = 41.6 ± 14.1 years) with normal or corrected-to-normal vision (6/9 or better in both eyes) participated in the study. Written, informed consent was obtained in the presence of a witness prior to testing according to a protocol approved by the Alfred Human Research Ethics Committee and Monash University Human Research Ethics Committee. The research was conducted in accordance with the Declaration of Helsinki. Visual acuity was assessed with a Snellen chart from a distance of 3 m and handedness with the Edinburgh Handedness Inventory.<sup>53</sup> All participants including healthy controls had their diagnostic status confirmed according to DSM-IV criteria with the Mini International Neuropsychiatric Interview (MINI).<sup>54</sup> For healthy controls, medical and psychiatric history was screened using a brief questionnaire to exclude individuals with a psychiatric disorder (e.g., BD, SCZ or MDD), neurological disorder (e.g., epilepsy), brain injury, or visual disorders (e.g., strabismus, amblyopia or colour vision deficiency). They were also screened to exclude those with first-degree relatives with a psychiatric disorder. For BD subjects, there was a similar medical screening and exclusion procedure, as well as screening with the MINI, to exclude those with co-morbid psychiatric disorders.

Formal state, trait, and clinical ratings were assessed with psychometric measures prior to the testing session for all subjects (see Section 2.2). Trait anxiety and state anxiety were assessed with the State-Trait Anxiety Inventory (STAI)<sup>55</sup> and premorbid intelligence was estimated with the Wechsler Test of Adult Reading (WTAR).<sup>56</sup> Severity of depressive and manic symptoms was assessed with the Montgomery-Åsberg Depression Scale (MÅDRS)<sup>57</sup> and Young Mania Rating Scale (YMRS),<sup>58</sup> respectively. Subjective mood was assessed with a 10-point self-report visual analogue scale immediately prior to and after the testing session (1 = “the worst you have ever felt”

to 10 = “the best you have ever felt”). The findings pertaining to the between-group comparisons of demographic and psychometric measures, and their association with EM measures, are reported in the Supporting Information Results.

All subjects with BD were outpatients at the time of testing, with varying degrees of symptom severity rating on the MÅDRS and YMRS, ranging between 0 and 24 and between 0 and 16, respectively (three subjects were moderate on the MÅDRS and two were moderate on the YMRS, based on the classifications of Snaith et al.<sup>59</sup> and McElroy et al.<sup>60</sup>). Most BD subjects (85%) reported a history of psychotic features. Regarding medication, three were unmedicated, one was on lithium only, one was on benzodiazepine only, and two were on atypical antipsychotics only. Of the remaining 13 BD subjects with combination therapy (eight of whom also used antidepressants), four received lithium, eight received sodium valproate, one received carbamazepine, two received benzodiazepine, and ten received atypical antipsychotics. Table 1 displays the demographic and psychometric data of the overall sample.

### 2.2 | Study protocol

Participants abstained from consuming caffeinated drinks, tobacco, and alcohol for 4 hours prior to testing given their known effects on BR rate<sup>7,61–64</sup> and EMs.<sup>65–68</sup> Each case-control pair comprised a subject with BD and a corresponding age- and sex-matched healthy control. Both subjects in each case-control pair completed an identical study protocol under supervision of an experimenter throughout testing to ensure task compliance. To avoid potential order effects, separate BR and EM tasks were run in counterbalanced order across four subgroups of case-control pairs (N = 5 pairs in each subgroup). For each subgroup, initially either the BR task or EM task was run, and they initially viewed BR using either the green or anaglyph drifting grating stimulus conditions (see Section 2.3). Therefore, each case-control pair completed all five primary BR stimulus conditions (see Section 2.3) and all six EM tasks (see Section 2.4), and both subjects in each case-control pair completed BR stimulus conditions and EM tasks in the same presentation order. All participants underwent an additional exploratory testing session on a separate day, assessing various exploratory BR stimulus conditions and EM measures (see Methods S1 and Results S1, and P. C. F. Law, S. M. Miller, & T. T. Ngo, in preparation).

### 2.3 | Apparatus, protocol and analysis for BR task

BR stimuli were generated with custom software programmed using Psychtoolbox-3<sup>69,70</sup> in conjunction with MATLAB™ (MathWorks Inc., Natick, MA, USA). The specific square-wave stimuli were as follows: (i) green stationary vertical and horizontal gratings; (ii) green rightward-drifting vertical and downward-drifting horizontal gratings; and (iii) red rightward-drifting vertical and blue downward-drifting horizontal gratings. The stimuli had a spatial frequency of 5.33 cycles/deg, were isoluminant between the two eyes, and were presented in a circular aperture subtending 1.5° of visual angle on a black background (stimulus contrast = 0.99). Drift speed was either 4 or 8 cycles/second.

**TABLE 1** Demographic, clinical and psychometric data for the overall sample

	Bipolar disorder (N=20)	Healthy controls (N=20)	P
Participants' characteristics			
Sex, male, n (%)	12 (60)	12 (60)	—
Age, years, mean±SD	41.6±13.4	41.6±14.1	.99 <sup>a</sup>
Right eye dominance, n (%)	13 (65)	13 (65)	1.00 <sup>b</sup>
Handedness, n (%)			.83 <sup>b</sup>
Left	2 (10)	1 (5)	—
Right	16 (80)	17 (85)	—
Ambidextrous	2 (10)	2 (10)	—
History of psychotic features, n (%)	17 (85)	—	—
Formal state ratings, mean±SD/median±MAD <sup>c</sup>			
Total STAI-state	41.2±12.5/38±9	31.6±9.6/29±6	8.00×10 <sup>-3*</sup>
Total MÅDRS	8.5±7.5/7±5.5	0.8±1.3/0±0	8.18×10 <sup>-6*</sup>
Total YMRS	6±5.7/4±4	0.3±0.7/0±0	3.36×10 <sup>-5*</sup>
Subjective mood: baseline	6.1±1.7/6±1	7.6±1.2/7.5±0.5	4.68×10 <sup>-3*</sup>
Subjective mood: post-test	5.7±1.8/5±1	7±1.4/7±1	3.04×10 <sup>-2*</sup>
Trait ratings, mean±SD/median±MAD			
Total STAI-trait	48.8±9/48±7	38.5±6.8/37±4	1.77×10 <sup>-4a,*</sup>
Total WTAR	114.6±10.2/117±4	119.9±3.5/119 ±1.5	5.96×10 <sup>-2c</sup>
Medication, n (%)			
No medication	3 (15)	—	—
Lithium only	1 (5)	—	—
Anticonvulsant only <sup>d</sup>	1 (5)	—	—
Atypical antipsychotics only <sup>e</sup>	2 (10)	—	—
Combination therapy (no antidepressants)	5 (25)	—	—
Lithium and antidepressants	2 (10)	—	—
Combination therapy and antidepressants	5 (25)	—	—
Atypical antipsychotics and antidepressants	1 (5)	—	—

All psychometric data collected in the exploratory testing session are reported in Table S7. SD, standard deviation; MAD, median absolute deviation; P, P value; STAI, State-Trait Anxiety Inventory; MÅDRS, Montgomery-Åsberg Depression Scale; YMRS, Young Mania Rating Scale; WTAR, Wechsler Test of Adult Reading.

<sup>a</sup>Independent-samples *t* test.

<sup>b</sup>Chi-squared test.

<sup>c</sup>Mann-Whitney *U* test.

<sup>d</sup>Benzodiazepine.

<sup>e</sup>Quetiapine, paliperidone, aripiprazole and olanzapine.

\**P*<.05 vs healthy controls.

The luminance of all stimuli (mean=1.02 cd/m<sup>2</sup>) and the background (0.35 cd/m<sup>2</sup>) was measured using an LS-100 luminance meter (Konica Minolta Sensing Americas Inc., Ramsey, NJ, USA) through passive polarizer filters (for green stimuli) and anaglyph monochrome filters (for red/blue stimuli) worn by the subject (detailed below). The five primary BR stimulus conditions were: (i) stationary green gratings; (ii) 4 cycles/second green gratings; (iii) 8 cycles/second green gratings; (iv) 4 cycles/second red/blue gratings; and (v) 8 cycles/second red/blue gratings. Additional exploratory BR stimulus conditions are described in the Supporting Information Methods.

Subjects were instructed to blink naturally and record what they observed passively (i.e., not to preferentially respond to any of the

percepts or try to influence their perceptions). Subjects pressed one raised key (V) on a standard keyboard in response to the left eye's presented image, and an adjacent raised key (B) in response to the right eye's presented image. A third response option (spacebar) was used to indicate response error and the perception of either mixed (e.g., checkerboard or mosaic image) or unusual percepts (e.g., filled circle or double images). BR testing was conducted in a quiet, dimly illuminated room. BR behavioural data collection was run with custom software generated in MATLAB™ (MathWorks Inc., Natick, MA, USA) for Windows 7™ on a customized desktop computer (see below).

After familiarizing subjects with the BR task, the BR testing session involved multiple 7-minute blocks (see below), each comprising

four 100-second trials. The blocks were separated by 110-second rest breaks and the trials by 30-second rest breaks. The first few minutes of BR viewing have been characterized by increases in BR rate within individuals.<sup>4,13,71-76</sup> However, BR rates stabilize with longer BR viewing periods,<sup>9,14</sup> yielding a more accurate recording of an individual's BR rate. Therefore, the first BR block in the testing session served to adequately stabilize BR rates for the remaining test blocks and familiarize the subject with the task to diminish the effects of any response errors. The BR stimulus presented for the stabilization block (Block 1) was identical to that displayed for the subsequent test block (Block 2; further details below). To avoid potential order effects, stimulus type (green gratings and anaglyph gratings) and drift speed (4 and 8 cycles/second) were counterbalanced across case-control pairs, with drift speed of each stimulus type grouped together.

The BR testing session comprised six recording blocks: (i) an initial stabilization block (Block 1); (ii) four test blocks, one for each drifting BR stimulus condition (Blocks 2-5); followed by (iii) one test block of stationary green gratings (Block 6). Blocks 1 and 2 involved the same stimulus being presented (as mentioned above), while a different stimulus was presented in each of the remaining four blocks, thus making a total of five different BR stimulus conditions. The four drifting grating BR stimulus conditions in Blocks 2-5 had a velocity of 4 or 8 cycles/second, which were counterbalanced within each stimulus type (green and anaglyph gratings) across the four subgroups. Within each subgroup, each case-control pair viewed an identical drifting BR stimulus condition for Blocks 1-2. For Blocks 3-5, case-control pairs within each subgroup completed the remaining (respective) three drifting BR stimulus conditions, which were counterbalanced across case-control pairs within the subgroup. For Block 6, all case-control pairs viewed stationary green gratings.

All green BR stimuli were dichoptically presented using a specialized 19-inch dual-screen LCD monitor (True3Di™; Sharper Technology Inc., Palo Alto, CA, USA; 60 Hz frame rate, 1280×1024 pixel resolution). Each screen was directly behind one of two linear polarizers oriented at right angles to each other, and a half-silvered mirror (beam-combiner) oriented at a 45° angle was between the polarizers. The BR stimulus comprised two conflicting images: green vertical gratings and green horizontal gratings. The vertical gratings drifted rightwards and the horizontal gratings downwards. To induce BR, conflicting images were independently and simultaneously presented at corresponding central positions on separate screens that projected each image in orthogonal planes (angles) of polarization. One image was transmitted through the half-silvered mirror while the adjacent image was reflected off the mirror, resulting in an interleaved (superimposed) stimulus of two orthogonally polarized images when naturally viewed.<sup>23</sup> Subjects viewed the polarized stimulus through passive linear polarizer filters at eye level from a distance of 3 m, resulting in the presentation of conflicting images to corresponding retinal locations of both eyes. Each polarizer filter was tuned to a distinct plane of polarization that enabled the exclusive presentation of one image to one eye while blocking its presentation to the other eye. The result was that, simultaneously, the left eye always viewed vertical gratings and the right eye always viewed horizontal gratings. The True3Di™ monitor was used to present green

BR stimuli and a 24-inch single-screen LCD monitor (P2412H; Dell Inc., Round Rock, TX, USA; 60 Hz frame rate, 1280×1024 pixel resolution) was used to simultaneously display the trial-based BR data collection protocol to the experimenter. Both monitors were connected to a customized desktop computer (Vostro 460 mini-tower; Dell Inc., Round Rock, TX, USA; see Supporting Information Methods).

All red/blue anaglyph BR stimuli were presented on a conventional 21.6-inch single-screen LCD monitor (X213W; Acer Inc., New Taipei City, Taiwan; 60 Hz frame rate, 1920×1080 pixel resolution) connected to a laptop (Pavilion dv6-6138tx; HP Inc., Palo Alto, CA, USA). The stimulus comprised two conflicting images: red rightward-drifting vertical gratings and blue downward-drifting horizontal gratings. Both images were simultaneously and centrally displayed on the LCD screen, resulting in a superimposed stimulus of two complementary colour images when naturally viewed. To present conflicting images at the same retinal region of both eyes, subjects viewed the BR stimulus through cardboard-framed red and blue monochrome filters at eye level from a distance of 3 m. Viewing the stimulus through these anaglyph glasses resulted in the left eye being presented with the red image and the right eye being simultaneously presented with the blue image.

The passive linear polarizer and red/blue anaglyph methods for dichoptic viewing have negligible crosstalk and, when viewed with the head in a neutral position, there is minimal ghosting (i.e., the subjective perceptual consequence of crosstalk, whereby there is faint perception in one eye of the other eye's intended image; see Law et al.<sup>23</sup>). To ensure that BR viewing was not influenced by the effects of ghosting, subjects were instructed (i) not to tilt or rotate their head, and (ii) to view the rivalry stimulus through the centre of the polarizer/monochrome filters.

Analysis of subjects' BR data employed custom software developed in MATLAB™ (MathWorks Inc., Natick, MA, USA). Stabilization blocks in each testing session were excluded from the analysis. BR rate was calculated by dividing the total number of perceptual alternations by the total time of BR viewing (expressed in Hz), excluding mixed/mosaic/unusual percepts and erroneous responses (i.e., incorrectly pressed key responses) which were all indicated by the subject pressing the spacebar. A spacebar response was treated in the analysis program by removal of the previous raised key press. Statistical analyses were performed with PASW Statistics 17 and R (version 3.2.5).<sup>77</sup>

## 2.4 | Apparatus, protocol and analysis for eye-movement tasks

The apparatus and protocol for each of the EM tasks in the current study were identical to those used and fully detailed in Law et al.<sup>51</sup> These EM tasks examined basic reflexive processes (prosaccades), inhibitory processes (antisaccades), anticipatory processes (predictive saccades), timing processes (self-paced saccades), voluntary saccades generated during free viewing of natural textures, and smooth-pursuit tracking. The target was a green cross subtending 1° of visual angle. The luminance of the target (mean=2.57 cd/m<sup>2</sup>) and background (0.16 cd/m<sup>2</sup>) was measured using a ColorCAL MKII Colorimeter

(Cambridge Research Systems Ltd., Rochester, UK). The target was presented on the screen for antisaccade, anticipatory, self-paced, prosaccade, and smooth-pursuit tasks. In addition to these measures detailed in Law et al.,<sup>51</sup> the present experiment analysed eye blink frequency during the free viewing of natural textures; however, this aspect did not change the EM data collection protocol.

In keeping with Hancock et al.'s<sup>50</sup> findings and anomalous EM profiles that have been reported in BD, there were six primary EM measures in the current study: (i) saccade rate during free viewing of natural textures; (ii) percentage of gap antisaccade errors; (iii) percentage of step antisaccade errors; (iv) predictive primary saccade gain; (v) maintenance pursuit gain on the constant velocity smooth-pursuit task; and (vi) maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task.

All of the EM analyses in the current study were identical to those of our previous study (Law et al.<sup>51</sup>), with the exception of compensatory saccade frequency in the smooth-pursuit task and saccade rate in the self-paced task. The frequency of compensatory saccades was calculated by combining the frequency of four saccade types (i.e., catch-up, predictive, backup, and square-wave jerks) identified using the criteria detailed in Law et al.<sup>51</sup> For the self-paced task, the overall saccade rate was calculated because saccade rate was not significantly different between  $\pm 2^\circ$  and  $\pm 7^\circ$  conditions in either BD or controls (Wilcoxon signed rank test,  $P \geq .46$ ). In addition to the measures detailed in Law et al.,<sup>51</sup> the frequency of eye blinks during the free viewing of natural textures was calculated in the current study. The rationale for using Bayes factors corresponding to the correlation between EMs and BR rate is fully detailed in Law et al.<sup>51</sup> In brief, Bayes factors were employed to assess the level of evidence (single sample *t* test), either for the null hypothesis that there was no correlation or for the alternative hypothesis that there was some non-zero correlation coefficient (e.g., a negative or positive correlation). For the between-group comparisons of BR rate and primary EM measures, Jeffreys–Zellner–Siow Bayes factors<sup>78</sup> were calculated to assess the level of evidence (two-sample *t* test)—either for the null hypothesis (i.e., that there was no group difference) or the alternative hypothesis (i.e., that there was a group difference). The remaining (13) EM measures were exploratory and are reported in the Supporting Information Methods and Results.

### 3 | RESULTS

#### 3.1 | Group comparisons of BR rate

BR rate was compared between BD patients and controls, to establish whether it was slower in the BD group before proceeding to compare EM measures. Normality was violated for the distributions of BR rate (Shapiro–Wilk test;  $P < .05$ ), and therefore multiple non-parametric (Mann–Whitney *U* test) comparisons were performed on BR rate between BD patients and controls for the five primary BR stimulus conditions. BR rate was significantly slower in BD patients than in controls across all the primary stimulus conditions ( $P \leq 1.16 \times 10^{-3}$ ; Bonferroni-adjusted  $\alpha$ :  $0.05/5 = 0.01$ ), except for stationary green gratings and 8

cycles/second anaglyph gratings ( $P \geq 1.22 \times 10^{-2}$ ). The corresponding Bayes factors indicate substantial evidence ( $3 < BF_{10} \leq 10$ ) to strong evidence ( $10 < BF_{10} \leq 30$ ) for a group difference in BR rate across all drifting primary stimulus conditions. For stationary green gratings, corresponding Bayes factors indicate weak evidence ( $1 < BF_{01} \leq 3$ ) in favour of the null hypothesis of no group difference. Thus, overall BR rate was found to be slower in the BD group than in the healthy group for the majority of primary stimulus conditions. These results along with other detailed findings relevant to stimulus optimization are reported and discussed elsewhere (P. C. F. Law, S. M. Miller, & T. T. Ngo, in preparation).

#### 3.2 | Group comparisons of primary eye-movement measures

Having established that BR rate was slow in BD, the primary EM measures were compared between BD patients and controls. Normality was violated for the distributions of primary EM measures (Shapiro–Wilk test;  $P < .05$ ), and therefore multiple non-parametric (Mann–Whitney *U* test) comparisons were performed between BD patients and controls for the six primary EM measures. Table 2 shows no significant group difference across all primary EM measures ( $P \geq 1.32 \times 10^{-2}$ ; Bonferroni-adjusted  $\alpha$ :  $0.05/6 = 8.33 \times 10^{-3}$ ). The corresponding Bayes factors indicate weak evidence ( $1 < BF_{01} \leq 3$ ) in favour of the null hypothesis of no group difference for all primary EM measures (see Table 2), with the exception of saccade rate on the free-viewing task, in which corresponding Bayes factors indicate substantial evidence ( $3 < BF_{10} \leq 10$ ) for a group difference. Thus, saccade rate on the free-viewing task was found to be lower in the BD group than in the healthy group, while no group difference was found for the remaining primary EM measures. The results pertaining to group comparisons of exploratory EM measures, in which no group difference was found for any exploratory EM measure, are reported in the Supporting Information Results, as are subjective mood and clinical state ratings (i.e., STAI-trait, STAI-state, MÅDRS and YMRS).

#### 3.3 | Relationship between primary eye-movement measures and BR rate

The association between each primary EM measure and BR rate was assessed in BD patients and controls, to examine whether there is a relationship between these EMs and slow BR rate in BD. Non-parametric (Spearman's  $\rho$ ) correlations were performed between all six primary EM measures and BR rate for the five primary stimulus conditions in both subject groups. Table 3 shows that there was no significant correlation between any primary EM measure and BR rate across all primary stimulus conditions in BD patients and controls ( $P \geq 7.87 \times 10^{-3}$ ; Bonferroni-adjusted  $\alpha$ :  $0.05/30 = 1.67 \times 10^{-3}$ ). In particular, the saccade rate on the free-viewing task was not significantly correlated with BR rate in either the BD or control group ( $P \geq 4.76 \times 10^{-2}$ , one-tailed; see Figure 2). Table 3 also shows that for all correlations in BD patients and most correlations in controls (90%; including all correlations for the free-viewing saccade rate), corresponding Bayes factors indicate either weak evidence ( $1 < BF_{01} \leq 3$ ) or substantial evidence ( $3 < BF_{01} \leq 10$ )

**TABLE 2** Comparison of average values for primary eye-movement measures between bipolar disorder subjects and healthy controls

	Bipolar disorder	Healthy controls		
	Median±MAD	Median±MAD	<i>P</i>	BF <sub>01</sub>
Free-viewing task				
Saccade rate (saccades/second)	2.42±0.42	2.65±0.26	1.32×10 <sup>-2</sup>	0.19
Antisaccade task				
% of total step errors	21.53±11.11	18.06±10.42	0.24	1.83 <sup>b</sup>
% of total gap errors	43.06±15.28	37.50±12.50	0.14	1.34 <sup>b</sup>
Anticipatory task				
Predictive primary saccade gain <sup>a</sup>	0.73±1.05	0.96±0.64	0.35	2.52 <sup>b</sup>
Smooth-pursuit task: constant				
Maintenance gain	0.95±0.03	0.98±0.03	8.10×10 <sup>-2</sup>	1.93 <sup>b</sup>
Smooth-pursuit task: sinusoidal				
Maintenance gain	1.37±0.39	1.18±0.17	0.23	1.36 <sup>b</sup>

Primary eye-movement (EM) measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining EM measures are exploratory. For exploratory EM measures, no significant between-group difference was found (see Table S1). The corresponding Bayes factors indicated weak evidence ( $1 < \text{BF}_{10} \leq 3$ ) for a group difference in compensatory saccade frequency on the constant velocity smooth-pursuit task (see Table S1). In contrast, there was weak evidence ( $1 < \text{BF}_{01} \leq 3$ ) or substantial evidence ( $3 < \text{BF}_{01} \leq 10$ ) in favour of the null hypothesis of no group difference for the remaining exploratory EM measures according to Bayes factors. °/s, degrees/second; MAD, median absolute deviation; *P*, *P* value (Mann–Whitney *U* test; two-tailed); BF<sub>01</sub>, Bayes factor value for null hypothesis of there being no group difference.

<sup>a</sup>For predictive saccades.

<sup>b</sup>More data (i.e., power) required to evaluate competing hypotheses.

in favour of the null hypothesis of no association between primary EMs and BR rate, rather than the alternative hypothesis (i.e., that there was an association<sup>79</sup>). There was, however, substantial evidence ( $3 < \text{BF}_{10} \leq 10$ ) for an association between maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task and BR rate, but only for select primary stimulus conditions in the control group (e.g., stationary and 8 cycles/second green gratings; with decisive evidence for 8 cycles/second green gratings, i.e.,  $\text{BF}_{10} > 100$ ). Thus, a decrease in maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task was associated with a slower BR rate for select primary stimulus conditions in the healthy group, while no relationship was found between any of the remaining primary EM measures and BR rate in both the BD and healthy groups. Detailed findings pertaining to the relationship between exploratory EM measures and BR rate—in which no significant association was found for most exploratory EM measures in either the BD or healthy group—are reported in the Supporting Information Results, as are the non-significant findings regarding the relationship between primary/exploratory EM measures, psychometric assessment ratings and medication.

## 4 | DISCUSSION

The current study investigated the relationship between EMs and BR rate in BD and healthy individuals, with a secondary aim of examining

differences in EM profiles between these groups. Each individual's EMs were recorded during various EM tasks (e.g., free viewing, antisaccade, anticipatory and smooth pursuit), and their BR rates were separately determined for BR tasks with different stimulus types and drift speeds. No significant relationship was found between EMs and BR rate, for each EM task across all BR stimulus conditions, in either the BD or the healthy group. Bayes factors supported this null hypothesis for most EM measures and, of particular relevance, there was support for no relationship between saccade rate on the free-viewing task and BR rate in both the BD and healthy groups. Importantly, there were no EM measures for which Bayes factors supported an association with BR rate in either the BD group or the control group, where those EMs were also different *between* the BD and healthy groups according to Bayes factors. These findings—together with a slower BR rate in the BD compared with the healthy group—provide evidence that EM profiles do not explain the slow BR endophenotype for BD.

Regarding the secondary issue of group differences in EMs, there was no significant group difference for primary EM measures of antisaccade, anticipatory, and smooth-pursuit tasks. Bayes factors supported these findings. These results contribute to the limited and conflicting literature on EM profiles in BD, and are in contrast to previous reports indicating that BD is associated with increased antisaccade error<sup>37-40</sup> (c.f. Fukushima et al.<sup>80</sup>), deficits in predictive primary saccade gain<sup>36</sup> (c.f. Crawford et al.<sup>41</sup>), and impaired maintenance pursuit gain<sup>32-35</sup> (c.f. Lencer et al.<sup>42</sup> and Moates et al.<sup>43</sup>).

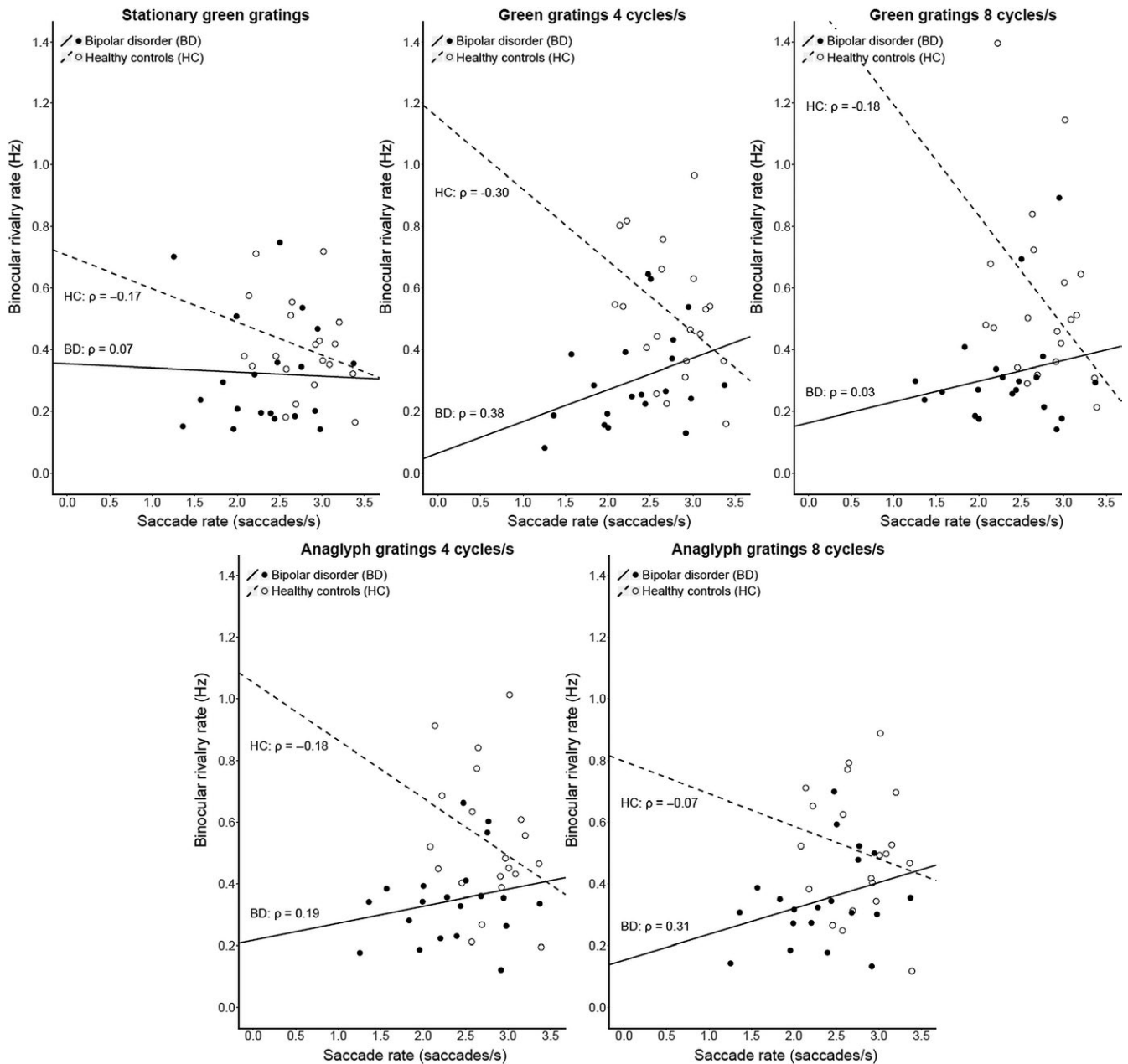
**TABLE 3** Relationship between primary eye-movement measures and binocular rivalry rate for the primary stimulus conditions in bipolar disorder subjects and healthy controls

	Stationary green gratings			4 cycles/s green gratings			8 cycles/s green gratings			4 cycles/s anaglyph gratings			8 cycles/s anaglyph gratings			
	$\rho$	P	BF <sub>01</sub>	$\rho$	P	BF <sub>01</sub>	$\rho$	P	BF <sub>01</sub>	$\rho$	P	BF <sub>01</sub>	$\rho$	P	BF <sub>01</sub>	
<b>Bipolar disorder</b>																
<b>Free-viewing task</b>																
Saccade rate (saccades/s) <sup>a</sup>	0.07	.38	3.57	0.38	0.38	4.76×10 <sup>-2</sup>	1.32 <sup>c</sup>	0.03	.46	2.64 <sup>c</sup>	0.19	.21	2.48 <sup>c</sup>	0.31	9.42×10 <sup>-2</sup>	1.66 <sup>c</sup>
<b>Antisaccade task</b>																
% of total step errors	0.02	.93	3.17	0.12	.63	2.63 <sup>c</sup>	2.63 <sup>c</sup>	-0.12	.60	3.59	0.02	.93	3.60	0.13	.57	2.99 <sup>c</sup>
% of total gap errors	-0.04	.87	2.97 <sup>c</sup>	0.06	.80	2.62 <sup>c</sup>	2.62 <sup>c</sup>	-0.09	.70	3.42	-0.13	.58	3.40	0.06	.82	3.17
<b>Anticipatory task</b>																
Predictive primary saccade gain <sup>b</sup>	0.26	.30	2.78 <sup>c</sup>	-0.07	.79	3.56	3.56	0.44	6.86×10 <sup>-2</sup>	2.76 <sup>c</sup>	-0.10	.70	3.03	0.03	.91	3.59
<b>Smooth-pursuit task: constant</b>																
Maintenance gain	-0.04	.86	2.82 <sup>c</sup>	0.04	.88	3.61	3.61	-0.35	.13	2.77 <sup>c</sup>	0.07	.78	3.55	0.15	.53	3.60
<b>Smooth-pursuit task: sinusoidal</b>																
Maintenance gain	-0.42	6.77×10 <sup>-2</sup>	3.24	-0.05	.85	3.58	3.58	-0.20	.40	3.53	0.05	.83	3.54	-0.07	.77	3.61
<b>Healthy controls</b>																
<b>Free-viewing task</b>																
Saccade rate (saccades/s) <sup>a</sup>	-0.17	0.24	2.14 <sup>c</sup>	-0.30	.10	1.36 <sup>c</sup>	1.36 <sup>c</sup>	-0.18	.22	1.93 <sup>c</sup>	-0.18	.22	2.16 <sup>c</sup>	-0.07	.38	2.94 <sup>c</sup>
<b>Antisaccade task</b>																
% of total step errors	0.05	0.82	3.27	0.24	.32	2.86 <sup>c</sup>	2.86 <sup>c</sup>	0.25	.28	2.72 <sup>c</sup>	0.09	.71	3.37	0.19	.43	3.09
% of total gap errors	0.10	0.68	3.53	0.25	.30	3.38	3.38	0.31	.19	3.26	0.19	.42	3.37	0.29	.21	3.10
<b>Anticipatory task</b>																
Predictive primary saccade gain <sup>b</sup>	-0.11	0.67	3.61	-0.05	.86	3.39	3.39	0.00	1.00	3.59	0.09	.73	3.12	-0.05	.86	3.59
<b>Smooth-pursuit task: constant</b>																
Maintenance gain	-0.09	0.71	2.53 <sup>c</sup>	-0.17	.47	2.88 <sup>c</sup>	2.88 <sup>c</sup>	-0.22	0.36	1.27 <sup>c</sup>	-0.08	.73	3.58	-0.16	.51	2.88 <sup>c</sup>
<b>Smooth-pursuit task: sinusoidal</b>																
Maintenance gain	0.42	6.45×10 <sup>-2</sup>	0.08	0.38	9.94×10 <sup>-2</sup>	0.38 <sup>c</sup>	0.38 <sup>c</sup>	0.47	4.69×10 <sup>-2</sup>	9.94×10 <sup>-4</sup>	0.41	7.57×10 <sup>-2</sup>	1.30 <sup>c</sup>	0.58	7.87×10 <sup>-3</sup>	1.03 <sup>c</sup>

Primary eye-movement (EM) measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining EM measures are exploratory. No significant correlation was found between the primary EM measures and binocular rivalry rate for any exploratory stimulus condition in either bipolar disorder subjects or healthy controls (see Table S2). For exploratory EM measures, no significant correlation was found with binocular rivalry rate for the primary or exploratory stimulus conditions in either bipolar disorder subjects or healthy controls (see Tables S3 and S4). The corresponding Bayes factors indicated either weak evidence ( $1 < \text{BF}_{01} \leq 3$ ) or substantial evidence ( $3 < \text{BF}_{01} \leq 10$ ) in favour of the null hypothesis of no association between EMs and binocular rivalry rate for most correlations in both groups (see Tables S5 and S6), cycles/s, saccades/second;  $\rho$ , Spearman's  $\rho$ ; P, value; BF<sub>01</sub>, Bayes factor value for null hypothesis of there being no correlation.

<sup>a</sup>One-tailed (two-tailed for all other measures).  
<sup>b</sup>For predictive saccades.  
<sup>c</sup>More data (i.e., power) required to evaluate competing hypotheses.





**FIGURE 2** Scatterplots showing the association between an individual's saccade rate during free viewing of natural textures and their binocular rivalry rate for the five primary stimulus conditions. Binocular rivalry rate (Hz) is denoted along the y-axis and the saccade rate (saccades/second) along the x-axis. Filled and hollow circles denote the individual data points for bipolar disorder (BD) subjects and healthy controls, respectively. Solid and dashed lines indicate the line of best fit from orthogonal linear regression for BD subjects and healthy controls, respectively. No significant association was observed between free-viewing saccade rate and binocular rivalry rate for all stimulus conditions in BD subjects and healthy controls (refer to Table 3). This pattern of non-significant results was verified with Bayes factors. Thus, no relationship was found between free-viewing saccade rate and binocular rivalry rate in BD subjects and healthy controls for the primary stimulus conditions. This finding—together with a slower binocular rivalry rate in BD subjects compared with healthy controls—provides evidence that free-viewing saccade rate does not explain the slow BR endophenotype for BD. cycles/s, cycles/second; saccades/s, saccades/second.  $\rho$ , Spearman's  $\rho$

However, this study is also the first to assess saccadic EMs on a free-viewing task in a BD cohort. While frequentist statistics showed no significant difference in free-viewing saccade rate between the BD and healthy groups, Bayes factors did provide support for a group difference, suggesting a lower free-viewing saccade rate in the BD group. This result, though, cannot explain the slow BR rate endophenotype for BD, because neither frequentist statistics nor Bayes factors suggested a

relationship between an individual's free-viewing saccade rate and their BR rate in either BD or healthy subjects across all stimulus conditions (including stationary gratings as used in Hancock et al.<sup>50</sup>). The combination of results overall supports slow BR in BD being a fundamental perceptual processing anomaly rather than a proxy measure of EM anomaly.

In the study by Hancock et al.,<sup>50</sup> the finding of a significant association between free-viewing saccade rate and BR rate in healthy

subjects was cited as support for a possible overlap between parietal brain regions relevant to both individual variation in BR rate and initiating shifts in eye position during free viewing of the environment. The current findings might appear to support such an overlap given the slow BR rate in BD and Bayes factor support for a low free-viewing saccade rate in BD, along with reports in the literature of parietal cortex anomalies in BD.<sup>81,82</sup> However, the overlapping parietal region interpretation is in fact *not* supported by the current findings because there was no association between free-viewing saccade rate and BR rate in the BD and control groups.

Although it cannot be ruled out that greater statistical power from a larger sample size may reveal significant relationships between EMs and BR rate within groups using frequentist statistics (see Supporting Information Results), the non-significant findings were verified with Bayes factors which overall supported the lack of association. Moreover, at a less conservative  $\alpha$  of 0.05, no significant correlation was observed for >95% of the correlational tests conducted between a primary EM measure and BR rate in the BD and control groups (as reported in the Supporting Information Results). This result indicates that the finding of no significant correlation between any primary EM measure and BR rate across all primary stimulus conditions in BD and controls is unlikely to have been due to chance alone. Nonetheless, greater statistical power might also reveal significant group differences with frequentist statistics, especially in the free-viewing saccade rate for which Bayes factors did support a group difference. The present correlational and comparative findings on EMs and BR rate were also not influenced by age, medication, premorbid intelligence, subjective mood, and clinical state (i.e., trait anxiety, state anxiety, severity of depressive and manic symptoms; see Supporting Information Results and Discussion). However, a larger sample size may reveal some influence of these variables. Finally, it is worth reiterating that all EM profiles examined in the current study were measured *separately* from BR viewing. It remains possible, therefore, that a relationship between EMs and BR rate may become evident if EMs are measured *during* BR viewing in BD and healthy cohorts.

The slow BR rate trait satisfies several criteria for being an endophenotype for BD (e.g., high sensitivity, heritability, and reliability)<sup>9,14-17</sup> and the current study adds to this endophenotype proposal by showing it is not explained by anomalous EMs in BD subjects. Future research on this trait will involve online BR testing, via a dedicated test website, to facilitate collection of the massive datasets required to properly assess its clinical and endophenotype potential.<sup>23</sup> Development of this online approach, along with stimulus optimization studies (P. C. F. Law, S. M. Miller, & T. T. Ngo, in preparation), will enable logistically feasible examination of the trait in a wide range of clinical, genetic, and molecular studies. Understanding of the trait will also be furthered by examining mechanisms of BR which remain elusive,<sup>11</sup> and this work may in turn inform understanding of mechanisms of BD. One such example is the pathophysiological model of BD originally proposed in reporting the slow BR trait<sup>15</sup>—a model based on hemispheric activation asymmetries and now being reconsidered in light of neuroimaging findings of white matter callosal deficits in BD.<sup>83-85</sup>

## 5 | CONCLUSIONS

This study provides evidence that EM profiles do not explain the slow BR trait in BD. The findings therefore argue against an interpretation in which slow BR in BD is considered a proxy variable for EM dysfunction in BD. Rather, the results suggest that the slow BR endophenotype reflects anomalous perceptual processing per se in BD. The study also contributes to the limited available data on EM profiles in BD by showing: (i) support for the free-viewing saccade rate being lower in BD patients than in healthy controls (albeit with no association between this measure and BR rate), and (ii) support for other EMs being normal in BD patients. Slow BR remains a candidate endophenotype for BD, whereby the trait can be applied in large-scale clinical and genetic studies to interrogate molecular and systems-level mechanisms underlying this debilitating psychiatric condition.

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## DISCLOSURES

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## REFERENCES

- Alais D, Blake R. *Binocular Rivalry*. Cambridge, MA: MIT Press; 2005.
- Blake R, Logothetis NK. Visual competition. *Nat Rev Neurosci*. 2002;3:13-21.
- Miller SM, ed. *The Constitution of Visual Consciousness: Lessons from Binocular Rivalry*. Amsterdam, The Netherlands: John Benjamins Publishing Company; 2013.
- Aafjes M, Heuting JE, Visser P. Individual and interindividual differences in binocular retinal rivalry in man. *Psychophysiology*. 1966;3:18-22.
- Breese BB. On inhibition. *Psychol Rev-Monogr S*. 1899;3:1-65.
- Enoksson P. Binocular rivalry and monocular dominance studied with optokinetic nystagmus. *Acta Ophthalmol*. 1963;41:544-563.
- George RW. The significance of the fluctuations experienced in observing ambiguous figures and in binocular rivalry. *J Gen Psychol*. 1936;15:39-61.
- McDougall W. The physiological factors of the attention-process. *Mind*. 1903;12:473-488.
- Miller SM, Hansell NK, Ngo TT, et al. Genetic contribution to individual variation in binocular rivalry rate. *Proc Natl Acad Sci USA*. 2010;107:2664-2668.
- Mull HK, Armstrong G, Telfer B. The effect of brightness upon reversible perspectives and retinal rivalry. *AJ Psychol*. 1956;69:123-125.

11. Ngo TT, Barsdell WN, Law PCF, Miller SM. *Binocular rivalry, brain stimulation and bipolar disorder*. In: Miller SM, ed. *The Constitution of Visual Consciousness: Lessons from Binocular Rivalry*. Amsterdam, The Netherlands: John Benjamins Publishing Company; 2013:211-252.
12. Wade NJ, Ngo TT. *Early views on binocular rivalry*. In: Miller SM, ed. *The Constitution of Visual Consciousness: Lessons from Binocular Rivalry*. Amsterdam, The Netherlands: John Benjamins Publishing Company; 2013:77-108.
13. Sy SL, Tomarken AJ, Patel V, Blake R. The time course of binocular rivalry during the phases of the menstrual cycle. *J Vis*. 2016;16:1-19.
14. Miller SM, Gynther BD, Heslop KR, et al. Slow binocular rivalry in bipolar disorder. *Psychol Med*. 2003;33:683-692.
15. Pettigrew JD, Miller SM. A 'sticky' interhemispheric switch in bipolar disorder? *P Roy Soc Lond B Bio*. 1998;265:2141-2148.
16. Nagamine M, Yoshino A, Miyazaki M, Takahashi Y, Nomura S. Difference in binocular rivalry rate between patients with bipolar I and bipolar II disorders. *Bipolar Disord*. 2009;11:539-546.
17. Vierck E, Porter RJ, Luty SE, et al. Further evidence for slow binocular rivalry rate as a trait marker for bipolar disorder. *Aust NZ J Psychiat*. 2013;47:371-379.
18. Zhu R, Ye X, Zhou X, Yang J, Yue Y, Wang K. Application of binocular competition paradigm in patients with bipolar disorder. *Chinese J Nerv Men Dis*. 2013;8:449-452.
19. Ewen JH. The psychological estimation of the effects of certain drugs upon the syntonix and schizophrenic psychoses: with a brief inquiry into a physiological basis of temperament. *J Ment Sci*. 1931;77:742-766.
20. Hunt JM, Guilford JP. Fluctuation of an ambiguous figure in dementia praecox and in manic depressive patients. *J Abnorm Soc Psych*. 1933;27:443-452.
21. Jia T, Ye X, Wei Q, et al. Difference in the binocular rivalry rate between depressive episodes and remission. *Physiol Behav*. 2015;151:272-278.
22. Shannon RW, Patrick CJ, Jiang Y, Bernat E, He S. Genes contribute to the switching dynamics of bistable perception. *J Vis*. 2011;11:1-7.
23. Law PCF, Paton BK, Thomson RH, Liu GB, Miller SM, Ngo TT. Dichoptic viewing methods for binocular rivalry research: prospects for large-scale clinical and genetic studies. *Twin Res Hum Genet*. 2013;16:1033-1078.
24. Miller SM, Ngo TT, van Swinderen B. Attentional switching in humans and flies: rivalry in large and miniature brains. *Front Hum Neurosci*. 2012;5:1-17.
25. Ngo TT, Mitchell PB, Martin NG, Miller SM. Psychiatric and genetic studies of binocular rivalry: an endophenotype for bipolar disorder? *Acta Neuropsychiatr*. 2011;23:37-42.
26. Gooding DC, Basso MA. The tell-tale tasks: a review of saccadic research in psychiatric patient populations. *Brain Cogn*. 2008;68:371-390.
27. Ivleva EI, Morris DW, Moates AF, Suppes T, Thaker GK, Tamminga CA. Genetics and intermediate phenotypes of the schizophrenia – Bipolar disorder boundary. *Neurosci Biobehav R*. 2010;34:897-921.
28. Levy DL, Holzman PS, Matthyse S, Mendell NR. Eye tracking dysfunction and schizophrenia: a critical perspective. *Schizophrenia Bull*. 1993;19:461-505.
29. O'Driscoll GA, Callahan BL. Smooth pursuit in schizophrenia: a meta-analytic review of research since 1993. *Brain Cogn*. 2008;68:359-370.
30. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45:984-994.
31. Carvalho N, Laurent E, Noiret N, et al. Eye movement in unipolar and bipolar depression: a systematic review of the literature. *Front Psychol*. 2015;6:1-19.
32. Ivleva EI, Moates AF, Hamm JP, et al. Smooth pursuit eye movement, prepulse inhibition, and auditory paired stimuli processing endophenotypes across the schizophrenia-bipolar disorder psychosis dimension. *Schizophr Bull*. 2014;40:642-652.
33. Sweeney JA, Luna B, Haas GL, Keshavan MS, Mann JJ, Thase ME. Pursuit tracking impairments in schizophrenia and mood disorders: step-ramp studies with unmedicated patients. *Biol Psychiat*. 1999;46:671-680.
34. Lencer R, Trillenber K, Trillenber-Krecker K, et al. Smooth pursuit deficits in schizophrenia, affective disorder and obsessive-compulsive disorder. *Psychol Med*. 2004;34:451-460.
35. Trillenber P, Sprenger A, Talamo S, et al. Visual and non-visual motion information processing during pursuit eye tracking in schizophrenia and bipolar disorder. *Eur Arch Psychiatry Clin Neurosci* 2016;267:225-235.
36. Keedy SK, Bishop JR, Weiden PJ, et al. Disease and drug effects on internally-generated and externally-elicited responses in first episode schizophrenia and psychotic bipolar disorder. *Schizophr Res*. 2014;159:101-106.
37. Gooding DC, Tallent KA. The association between antisaccade task and working memory task performance in schizophrenia and bipolar disorder. *J Nerv Ment Dis*. 2001;189:8-16.
38. Harris MSH, Reilly JL, Thase ME, Keshavan MS, Sweeney JA. Response suppression deficits in treatment-naïve first-episode patients with schizophrenia, psychotic bipolar disorder and psychotic major depression. *Psychiat Res*. 2009;170:150-156.
39. Tien AY, Ross DE, Pearlson G, Strauss ME. Eye movements and psychopathology in schizophrenia and bipolar disorder. *J Nerv Ment Dis*. 1996;184:331-338.
40. Martin LF, Hall M-H, Ross RG, Zerbe G, Freedman R, Olincy A. Physiology of schizophrenia, bipolar disorder, and schizoaffective disorder. *A J Psychiat*. 2007;164:1900-1906.
41. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L. Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. *Psychol Med*. 1995;25:461-471.
42. Lencer R, Reilly JL, Harris MS, Sprenger A, Keshavan MS, Sweeney JA. Sensorimotor transformation deficits for smooth pursuit in first-episode affective psychoses and schizophrenia. *Biol Psychiat*. 2010;67:217-223.
43. Moates AF, Ivleva EI, O'Neill HB, et al. Predictive pursuit association with deficits in working memory in psychosis. *Biol Psychiat*. 2012;72:752-757.
44. Blake RR, Fox R, McIntyre C. Stochastic properties of stabilized-image binocular rivalry alternations. *J Exp Psychol*. 1971;88:327-332.
45. Wade NJ. Binocular rivalry between single lines viewed as real images and afterimages. *Percept Psychophys*. 1975;17:571-577.
46. Wade NJ, Tatler BW. *The Moving Tablet of the Eye: The Origins of Modern Eye Movement Research*. New York, NY: Oxford University Press; 2005.
47. Wade NJ. The effect of orientation in binocular contour rivalry of real images and afterimages. *Percept Psychophys*. 1974;15:227-232.
48. van Dam LCJ, van Ee R. The role of saccades in exerting voluntary control in perceptual and binocular rivalry. *Vision Res*. 2006;46:787-799.
49. van Dam LCJ, van Ee R. Retinal image shifts, but not eye movements per se, cause alternations in awareness during binocular rivalry. *J Vis*. 2006;6:1172-1179.
50. Hancock S, Gareze L, Findlay JM, Andrews TJ. Temporal patterns of saccadic eye movements predict individual variation in alternation rate during binocular rivalry. *Iperception*. 2012;3:88-96.
51. Law PCF, Paton BK, Riddiford JA, Gurvich CT, Ngo TT, Miller SM. No relationship between binocular rivalry rate and eye-movement profiles in healthy individuals: a Bayes factor analysis. *Perception*. 2015;44:643-661.
52. Kathmann N, Hochrein A, Uwer R, Bondy B. Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. *Am J Psychiat*. 2003;160:696-702.
53. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9:97-113.

54. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview. *J Clin Psychiat* 1998;59:22-33.
55. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press; 1983.
56. Wechsler D. *Wechsler Test of Adult Reading (WTAR)*. San Antonio, TX: The Psychological Corporation; 2001.
57. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Brit J Psychiat*. 1979;134:382-389.
58. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Brit J Psychiat*. 1978;133:429-435.
59. Snaith RP, Harrop FM, Newby DA. Grade scores of the Montgomery-Åsberg depression and the clinical anxiety scales. *Brit J Psychiat*. 1986;148:599-601.
60. McElroy SL, Martens BE, Winstanley EL, Creech R, Malhotra S, Keck PEJ. Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. *J Affect Disorders*. 2010;124:157-163.
61. Bárány EH, Halldén U. The influence of some central nervous depressants on the reciprocal inhibition between the two retinae as manifested in retinal rivalry. *Acta Physiol Scand*. 1947;13:296-316.
62. Donnelly M, Miller RJ. Ingested ethanol and binocular rivalry. *Invest Opth Vis Sci*. 1995;36:1548-1554.
63. McDougall W, Smith M. *The Effects of Alcohol and Some Other Drugs During Normal and Fatigued Conditions*. London: HMS Office; 1920.
64. Seedorff HH. Effect of alcohol on the motor fusion reserves and stereopsis as well as on the tendency to nystagmus. *Acta Ophthalmol*. 1956;34:273-280.
65. Domino EF, Ni LS, Zhang H. Effects of tobacco smoking on human ocular smooth pursuit. *Clin Pharmacol Ther*. 1997;61:349-359.
66. Smith A, Brice C, Nash J, Rich N, Nutt DJ. Caffeine and central noradrenaline: effects on mood, cognitive performance, eye movements and cardiovascular function. *J Psychopharmacol*. 2003;17:283-292.
67. Thaker GK, Ellsberry R, Moran M, Lahti A, Tamminga C. Tobacco smoking increases square-wave jerks during pursuit eye movements. *Biol Psychiat*. 1991;29:82-88.
68. Wilkinson IMS, Kime R, Purnell M. Alcohol and human eye movement. *Brain Cogn*. 1974;97:785-792.
69. Brainard DH. The psychophysics toolbox. *Spat Vis*. 1997;10:433-436.
70. Pelli DG. The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat Vis*. 1997;10:437-442.
71. Cogan R, Goldstein AG. Reporting of fragmentations in the binocular rivalry of contours. *Am J Psychol*. 1972;85:569-584.
72. Goldstein AG. Retinal rivalry and Troxler's effect: a correlation. *Percept Psychophys*. 1968;4:261-263.
73. Hodges WF, Fox R. Effect of arousal and intelligence on binocular rivalry rate. *Percept Motor Skill*. 1965;20:71-75.
74. Hollins M. The effect of contrast on the completeness of binocular rivalry suppression. *Percept Psychophys*. 1980;27:550-556.
75. Suzuki S, Grabowecky M. Long-term speeding in perceptual switches mediated by attention-dependent plasticity in cortical visual processing. *Neuron*. 2007;56:741-753.
76. Freyberg J, Robertson CE, Baron-Cohen S. Reduced perceptual exclusivity during object and grating rivalry in autism. *J Vis*. 2015;15:1-12.
77. R Core Team. R: A language and environment for statistical computing. Vienna, Austria. 2016.
78. Rouder JN, Speckman PL, Sun D, Morey RD, Iverson G. Bayesian tests for accepting and rejecting the null hypothesis. *Psychon B Rev*. 2009;16:225-237.
79. Jeffreys H. *The Theory of Probability*, 3rd edn. Oxford, UK: Oxford University Press; 1961.
80. Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I. Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. *J Psychiat Res*. 1990;24:9-24.
81. Kanai R, Bahrami B, Rees G. Human parietal cortex structure predicts individual differences in perceptual rivalry. *Curr Biol*. 2010;20:1626-1630.
82. Lyoo IK, Sung YH, Dager SR, et al. Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disord*. 2006;8:65-74.
83. Cullen KR, Lim KO. Toward understanding the functional relevance of white matter deficits in bipolar disorder. *JAMA Psychiatry*. 2014;71:362-364.
84. Sarrazin S, Poupon C, Linke J, et al. A multicenter tractography study of deep white matter tracts in bipolar I disorder: psychotic features and interhemispheric disconnectivity. *JAMA Psychiatry*. 2014;71:388-396.
85. Miller SM. Vestibular neuromodulation: stimulating the neural crossroads of psychiatric illness. *Bipolar Disord* 2016;18:539-543.

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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## Supporting Information

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## **Supporting Information Methods**

All case-control pairs underwent an additional exploratory testing session on a separate day. The assessment protocol was identical to that in the first (primary) testing session in order to re-confirm an individual's diagnostic status and re-assess their formal state and clinical ratings. All subjects with BD were clinically stable outpatients at the time of testing, with varying degrees of symptom severity rating on the MÅDRS and YMRS (ranging between 0–39 and 0–18, respectively), with one subject who was severe on the MÅDRS (based on the classifications of Snaith, Harrop, & Newby<sup>1</sup>; see also McElroy et al.<sup>2</sup>).

The BR stimulus conditions presented in this exploratory testing session were oppositely drifting square-wave red-expanding rings and blue-contracting concentric rings, using the same stimulus characteristics as the red/blue anaglyph gratings (i.e., spatial frequency, luminance, size, color channels). Drift speed was either 4 or 8 cycles/s. The red/blue anaglyph rings were included on an exploratory basis as they have not previously been examined in clinical BR studies. Overall the red/blue anaglyph stimuli were assessed in addition to green gratings to validate the anaglyph method of BR testing for potential use in large-scale and online BR studies (Law et al.<sup>3</sup>; Law et al., in preparation). The stimulus presentation apparatus and protocol for anaglyph rings were identical to that for anaglyph gratings (i.e., the left eye always viewed the red image and the right eye always viewed the blue image), as were the BR viewing and behavioural response instructions (i.e., subjects pressed the V and B keys respectively in response to perceiving each corresponding image, and pressed the spacebar to indicate response error and in response to perceiving mixed or unusual percepts, e.g., checkerboard, mosaic, fill circle, or double images).

The exploratory testing session comprised ten recording blocks: (i) five blocks retesting the individual's drifting stimulus protocol as completed in the first (primary) BR testing session (i.e., drifting green and anaglyph drifting gratings; Blocks 1–5); followed by

(ii) one stabilization block and two test blocks of red/blue anaglyph rings at either 4 or 8 cycles/s (the drift speed presented for the stabilization block and subsequent test block was identical); and (iii) two test blocks of a coherence rivalry task (not relevant to or reported in the current study). To avoid potential order effects, the following were counterbalanced across case-control pairs (for Blocks 6–10): (i) 4 and 8 cycles/s anaglyph rings (together as a pair of testing blocks); (ii) BR using anaglyph rings and coherence rivalry task (as different stimulus conditions).

The customized desktop computer (Vostro 460 mini-tower; Dell Inc., Round Rock, TX, USA) used for simultaneously presenting BR stimuli and collecting behavioral data was fitted with a Gigabyte™ ATI Radeon HD 6850 video card, 8GB RAM, and Cooler Master™ eXtreme Power Plus 700W power supply unit. These modifications were to enable adequate processing capacity by the PC as it was connected to and concurrently running both the 19-inch True3Di™ monitor (Sharper Technology Inc., Palo Alto, CA, USA) — for green BR stimuli presentation — and a 24-inch single-screen LCD monitor (P2412H; Dell Inc., Round Rock, TX, USA) — for displaying the trial-based BR data collection protocol.

## **Supporting Information Results**

### Group comparisons in binocular rivalry rate for exploratory stimulus conditions

BR rate was compared between BD and controls for exploratory stimulus conditions, to establish whether it was slower in the BD group before proceeding to compare exploratory EM measures. Normality was violated for the distributions of BR rate (Shapiro-Wilk test;  $p < 0.05$ ), therefore multiple non-parametric (Mann-Whitney U test) comparisons were performed on BR rate between BD and controls for the two exploratory stimulus conditions. BR rate was significantly slower in BD patients than in controls for 4 and 8 cycles/s anaglyph rings ( $p \leq 1.44 \times 10^{-3}$ ; Bonferroni-adjusted  $\alpha$ :  $0.05/2 = 2.50 \times 10^{-2}$ ). The corresponding Bayes

factors indicate very strong evidence ( $30 < BF_{10} \leq 100$ ) and decisive evidence ( $BF_{10} > 100$ ) for a group difference in BR rate for 4 and 8 cycles/s anaglyph rings, respectively. Thus BR rate was found to be slower in the BD group than in the healthy group for these exploratory stimulus conditions.

#### Group comparisons in exploratory eye-movement measures

Having established that BR rate is slow in BD for these exploratory stimulus conditions, the exploratory EM measures were compared between BD and controls. Normality was violated for the distributions of exploratory EM measures (Shapiro-Wilk test;  $p < 0.05$ ), therefore multiple non-parametric (Mann-Whitney U test) comparisons were performed between BD and controls for the 13 exploratory EM measures. Table S1 shows no significant group difference across all exploratory EM measures ( $p \geq 8.10 \times 10^{-2}$ ; Bonferroni-adjusted  $\alpha$ :  $0.05/13 = 3.85 \times 10^{-3}$ ). However, corresponding Bayes factors indicate weak evidence ( $1 < BF_{10} \leq 3$ ) for a group difference in compensatory saccade frequency on the constant velocity smooth-pursuit task. For the remaining exploratory EM measures, there was either weak evidence ( $1 < BF_{01} \leq 3$ ) or substantial evidence ( $3 < BF_{01} \leq 10$ ) in favor of the null hypothesis of no group difference according to Bayes factors. Thus compensatory saccade frequency on the constant velocity smooth-pursuit task was found to be greater in the BD group than in the healthy group, while no group difference was found for the remaining exploratory EM measures.

A power analysis indicated that, assuming power of 0.80 and a conservative Bonferroni-adjusted  $\alpha$  of  $8.33 \times 10^{-3}$  ( $0.05/6$  comparative tests; two-tailed), the current study's sample size of 20 would be sufficient to detect a significant group difference in primary EM measures with a minimum true effect size of 1.19 (Gpower)<sup>4</sup>. Likewise, for exploratory EM measures, assuming power of 0.80 and a conservative Bonferroni-adjusted  $\alpha$  of  $3.85 \times 10^{-3}$



(0.05/13 comparative tests; two-tailed), the current study's sample size of 20 would be sufficient to detect a significant group difference with a minimum true effect size of 1.29.

*Table S1.* Comparison of average values for exploratory eye-movement measures between bipolar disorder and healthy controls.

	Bipolar disorder	Healthy controls	<i>p</i>	BF <sub>01</sub>
	Median ± <i>MAD</i>	Median ± <i>MAD</i>		
<b>Antisaccade task</b>				
Latency <sup>a</sup>	0.33 ± 0.04	0.30 ± 0.02	0.36	2.34 <sup>c</sup>
Primary saccade gain <sup>a</sup>	-0.04 ± 0.34	0.13 ± 0.15	8.10×10 <sup>-2</sup>	1.87 <sup>c</sup>
Final eye position gain <sup>a</sup>	0.86 ± 0.18	0.92 ± 0.06	0.58	1.43 <sup>c</sup>
<b>Anticipatory task</b>				
% of predictive saccades	8.33 ± 5.56	11.11 ± 4.17	0.53	2.69 <sup>c</sup>
Final eye position gain <sup>b</sup>	1.17 ± 0.24	1.06 ± 0.06	0.84	2.66 <sup>c</sup>
<b>Self-paced task</b>				
Saccade rate (saccades/s)	1.31 ± 0.22	1.16 ± 0.19	0.45	2.95 <sup>c</sup>
<b>Prosaccade task</b>				
Primary saccade gain	0.85 ± 0.07	0.85 ± 0.06	0.78	3.21
Final eye position gain	0.92 ± 0.05	0.92 ± 0.04	0.72	3.03
Latency	0.18 ± 0.01	0.20 ± 0.02	0.20	1.61 <sup>c</sup>
<b>Free-viewing task</b>				
Saccade amplitude (°/s)	2.61 ± 0.95	2.69 ± 0.53	0.70	2.96 <sup>c</sup>
Total eye blink frequency	19.00 ± 11.50	14.00 ± 12.50	0.43	1.98 <sup>c</sup>
<b>Smooth-pursuit task: Constant</b>				
Compensatory saccade frequency	261.50 ± 61	247.00 ± 42	0.23	0.91 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>				
Compensatory saccade frequency	262.50 ± 61	217.00 ± 41.50	0.30	1.03 <sup>c</sup>

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. saccades/s, saccades/second; °/s, degrees/second; *MAD*, Median absolute deviation; *p*, *p* value (Mann-Whitney U test; two-tailed); BF<sub>01</sub>, Bayes factors value for null hypothesis of there being no group difference.

<sup>a</sup> For antisaccades.

<sup>b</sup> For predictive saccades.

<sup>c</sup> More data (i.e., power) required to evaluate competing hypotheses.

### Relationship between primary eye-movement measures and binocular rivalry rate for exploratory stimulus conditions

The association between each primary EM measure and BR rate was assessed in BD and controls for exploratory stimulus conditions, to examine whether there is a relationship between these EMs and slow BR rate in BD. Non-parametric (Spearman's  $\rho$ ) correlation

analyses were performed between all six primary EM measures and BR rate for the two exploratory stimulus conditions in BD and controls. Table S2 shows no significant correlation between any primary EM measure and BR rate for 4 and 8 cycles/s anaglyph rings in BD and controls ( $p \geq 3.23 \times 10^{-2}$ ; Bonferroni-adjusted  $\alpha$ :  $0.05/12 = 4.17 \times 10^{-3}$ ). In particular, saccade rate on the free-viewing task was not significantly correlated with BR rate in either the BD or control group ( $p \geq 0.23$ , one-tailed; see *Figure S1*). For most correlations in both groups (~83% for BD and 75% for controls; see *Table S2*), corresponding Bayes factors indicate either weak evidence ( $1 < BF_{01} \leq 3$ ) or substantial evidence ( $3 < BF_{01} \leq 10$ ) in favor of the null hypothesis of no association between EMs and BR rate, rather than the alternative hypothesis (i.e., that there was an association<sup>5</sup>). There was however, substantial evidence ( $3 < BF_{10} \leq 10$ ) for an association between decreased maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task and slower BR rate for 8 cycles/s anaglyph rings, though only in controls. Thus a decrease in maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task was associated with a slower BR rate for one exploratory stimulus condition in the healthy group, whereas no relationship was found between the vast majority of primary EM measures and BR rate for exploratory stimulus conditions in both BD and healthy controls.

A power analysis indicated that, assuming power of 0.80 and a conservative Bonferroni-adjusted  $\alpha$  of  $1.67 \times 10^{-3}$  (0.05/30 correlational tests; two-tailed), the current study's sample size of 20 would be sufficient to detect a significant correlation between primary EM measures and BR rate with a minimum true effect size of 0.72 for primary stimulus conditions (Gpower)<sup>4</sup>. Likewise, assuming power of 0.80 and a conservative Bonferroni-adjusted  $\alpha$  of  $4.17 \times 10^{-3}$  (0.05/12 correlational tests; two-tailed), the current study's sample size of 20 would be sufficient to detect a significant correlation between

primary EM measures and BR rate with a minimum true effect size of 0.69 for exploratory stimulus conditions.

*Table S2.* Relationship between primary eye-movement measures and binocular rivalry rate for exploratory stimulus conditions in bipolar disorder and healthy controls.

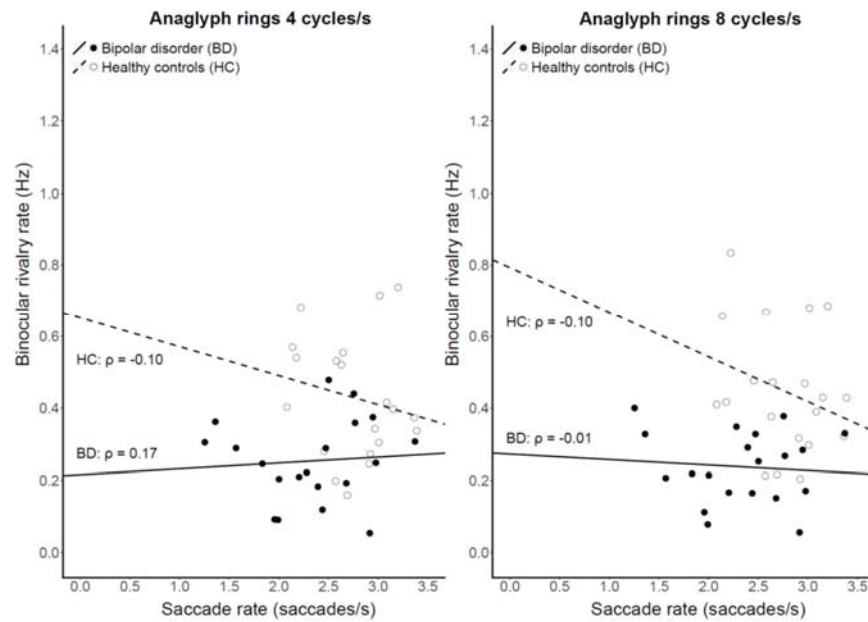
	4 cycles/s anaglyph rings			8 cycles/s anaglyph rings		
	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>
<i>Bipolar disorder</i>						
<b>Free-viewing task</b>						
Saccade rate (saccades/s) <sup>a</sup>	0.17	0.23	3.45	-0.01	0.48	3.41
<b>Antisaccade task</b>						
% of total step errors	-0.00	1.00	3.50	-0.29	0.21	1.81 <sup>c</sup>
% of total gap errors	0.02	0.95	3.30	-0.36	0.13	1.60 <sup>c</sup>
<b>Anticipatory task</b>						
Predictive primary saccade gain <sup>b</sup>	-0.08	0.75	2.91 <sup>c</sup>	-0.04	0.87	3.23
<b>Smooth-pursuit task: Constant</b>						
Maintenance gain	-0.26	0.27	0.65 <sup>c</sup>	-0.41	7.38×10 <sup>-2</sup>	0.37 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>						
Maintenance gain	0.01	0.99	1.75 <sup>c</sup>	-0.03	0.89	2.75 <sup>c</sup>
<i>Healthy controls</i>						
<b>Free-viewing task</b>						
Saccade rate (saccades/s) <sup>a</sup>	-0.10	0.35	2.93 <sup>c</sup>	-0.10	0.34	2.26 <sup>c</sup>
<b>Antisaccade task</b>						
% of total step errors	0.23	0.34	2.53 <sup>c</sup>	0.00	0.99	3.17
% of total gap errors	0.32	0.17	2.38 <sup>c</sup>	0.08	0.76	3.41
<b>Anticipatory task</b>						
Predictive primary saccade gain <sup>b</sup>	-0.20	0.43	3.22	-0.15	0.55	3.53
<b>Smooth-pursuit task: Constant</b>						
Maintenance gain	-0.31	0.19	0.62 <sup>c</sup>	-0.10	0.66	2.23 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>						
Maintenance gain	0.48	3.23×10 <sup>-2</sup>	0.35 <sup>c</sup>	0.25	0.30	0.15

Note. Primary eye-movement (EM) measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining EM measures are exploratory. For exploratory EM measures, no significant correlation was found with binocular rivalry rate for any primary or exploratory stimulus condition in either bipolar disorder or healthy controls (see *Tables S3* and *S4*). The corresponding Bayes factors indicate either weak evidence ( $1 < \text{BF}_{01} \leq 3$ ) or substantial evidence ( $3 < \text{BF}_{01} \leq 10$ ) in favor of the null hypothesis of no association between EMs and BR rate for most correlations in both groups (see *Tables S5* and *S6*). saccades/s, saccades/second; cycles/s, cycles/second;  $\rho$ , Spearman's  $\rho$ ;  $p$ ,  $p$  value; BF<sub>01</sub>, Bayes factors value for null hypothesis of there being no correlation.

<sup>a</sup> One-tailed (two-tailed for all other measures).

<sup>b</sup> For predictive saccades.

<sup>c</sup> More data (i.e., power) required to evaluate competing hypotheses.



*Figure S1.* Scatterplots showing the association between an individual’s saccade rate during free viewing of natural textures and their binocular rivalry rate for the exploratory stimulus conditions. Binocular rivalry rate (Hz) is denoted along the y-axis and the saccade rate (saccades/s) along the x-axis. Filled and hollow circles denote the individual data points for bipolar disorder (BD) subjects and healthy controls, respectively. Solid and dashed lines indicate the line of best fit from orthogonal linear regression for BD subjects and healthy controls, respectively (see also *Table S2* for the corresponding results). No significant association was observed between free-viewing saccade rate and binocular rivalry rate for 4 and 8 cycles/s anaglyph grating stimulus conditions in BD subjects and healthy controls. This pattern of non-significant results was verified with Bayes factors. Thus no relationship was found between free-viewing saccade rate and binocular rivalry rate in BD subjects and healthy controls for these exploratory stimulus conditions. This finding — together with a slower binocular rivalry rate in BD subjects compared with healthy controls — provides evidence that free-viewing saccade rate does not explain the slow BR endophenotype for BD. cycles/s, cycles/second; saccades/s, saccades/second;  $\rho$ , Spearman’s  $\rho$ .

### Relationship between exploratory eye-movement measures and binocular rivalry rate

The association between each exploratory EM measure and BR rate was assessed in BD and controls for both primary and exploratory stimulus conditions, to examine whether there is a relationship between these EMs and slow BR rate in BD. Non-parametric (Spearman's  $\rho$ ) correlation analyses were performed between all 13 exploratory EM measures and BR rate for the five primary stimulus conditions and the two exploratory stimulus conditions in BD and controls. *Tables S3* and *S4* show no significant correlation between any exploratory EM measure and BR rate across all primary and exploratory stimulus conditions in BD and controls, respectively ( $p \geq 2.57 \times 10^{-3}$ ; Bonferroni-adjusted  $\alpha$  for primary and exploratory stimulus conditions:  $0.05/65 = 7.69 \times 10^{-4}$  and  $0.05/26 = 1.92 \times 10^{-3}$ , respectively). For most correlations in both groups, corresponding Bayes factors indicate either weak evidence ( $1 < BF_{01} \leq 3$ ) or substantial evidence ( $3 < BF_{01} \leq 10$ ) in favor of the null hypothesis of no association between EMs and BR rate, rather than the alternative hypothesis (i.e., that there was an association<sup>5</sup>), for primary stimulus conditions (~97% for BD and ~85% for controls; see *Table S5*) and exploratory stimulus conditions (~81% for BD and ~73% for controls; see *Table S6*). However, Bayes factors indicated substantial evidence ( $3 < BF_{10} \leq 10$ ) for an association between prolonged antisaccade latency and slower BR rate across most primary stimulus conditions (e.g., stationary and 4 cycles/s green gratings, 4 and 8 cycles/s anaglyph gratings), though only in BD subjects. Further substantial evidence ( $3 < BF_{10} \leq 10$ ) for an association was found between the following EM measures and BR rate primary stimulus conditions in healthy controls: (i) between decreased percentage of predictive saccades and slower BR rate for all green-grating stimulus conditions; (ii) between increased primary saccade gain on the prosaccade task and slower BR rate for 8 cycles/s green gratings; (iii) between greater compensatory saccade frequency on the constant velocity smooth-pursuit task and slower BR rate for stationary and 8 cycles/s green gratings; and (iv) between greater

compensatory saccade frequency on the sinusoidal velocity smooth-pursuit task and slower BR rate for stationary and 8 cycles/s green gratings. For exploratory stimulus conditions, substantial evidence ( $3 < BF_{10} \leq 10$ ) for an association was found between higher saccade rate on the self-paced task and slower BR rate for 8 cycles/s anaglyph rings, though only in BD subjects. Therefore, although various exploratory EM measures were found to be associated with BR rate, no relationship was found between the majority of exploratory EM measures and BR rate for primary or exploratory stimulus conditions in both BD and healthy groups.

A power analysis indicated that, assuming power of 0.80 and a conservative Bonferroni-adjusted  $\alpha$  of  $7.69 \times 10^{-4}$  (0.05/65 correlational tests; two-tailed), the current study's sample size of 20 would be sufficient to detect a significant correlation between exploratory EM measures and BR rate with a minimum true effect size of 0.75 for the primary stimulus conditions (Gpower)<sup>4</sup>. Likewise, assuming power of 0.80 and a conservative Bonferroni-adjusted  $\alpha$  of  $1.92 \times 10^{-3}$  (0.05/26 correlational tests; two-tailed), the current study's sample size of 20 would be sufficient to detect a significant correlation between exploratory EM measures and BR rate with a minimum true effect size of 0.72 for the exploratory stimulus conditions.

Table S3. Relationship between exploratory eye-movement measures and binocular rivalry rate for primary and exploratory stimulus conditions in bipolar disorder.

	Stationary green gratings		4 cycles/s green gratings		8 cycles/s green gratings		4 cycles/s anaglyph gratings		8 cycles/s anaglyph gratings		4 cycles/s anaglyph rings		8 cycles/s anaglyph rings	
	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$
<b>Antisaccade task</b>														
Latency <sup>a</sup>	-0.64	2.57×10 <sup>-3</sup>	-0.64	2.57×10 <sup>-3</sup>	-0.54	1.47×10 <sup>-2</sup>	-0.48	3.17×10 <sup>-2</sup>	-0.50	2.50×10 <sup>-2</sup>	-0.36	0.12	-0.31	0.19
Primary saccade gain <sup>a</sup>	0.02	0.93	-0.00	1.00	0.17	0.47	0.28	0.23	0.13	0.60	-0.17	0.46	0.24	0.32
Final eye position gain <sup>a</sup>	0.18	0.46	0.27	0.25	0.09	0.72	0.15	0.53	0.29	0.22	-0.08	0.74	0.01	0.99
<b>Anticipatory task</b>														
% of predictive saccades	0.35	0.13	0.32	0.16	0.04	0.86	0.27	0.25	0.31	0.18	0.54	1.36×10 <sup>-2</sup>	0.45	4.44×10 <sup>-2</sup>
Final eye position gain <sup>b</sup>	0.42	8.61×10 <sup>-2</sup>	0.15	0.55	0.19	0.45	0.03	0.89	-0.08	0.77	0.01	0.96	-0.02	0.93
<b>Self-paced task</b>														
Saccade rate (saccades/s) <sup>c</sup>	0.07	0.39	0.08	0.37	-0.01	0.49	0.04	0.43	0.08	0.37	-0.43	2.87×10 <sup>-2</sup>	-0.56	5.34×10 <sup>-2</sup>
<b>Prosaccade task</b>														
Primary saccade gain	-0.16	0.50	0.08	0.73	-0.16	0.50	0.07	0.76	0.09	0.71	-0.25	0.30	-0.12	0.62
Final eye position gain	0.23	0.34	0.24	0.31	0.11	0.65	0.24	0.30	0.22	0.36	-0.12	0.62	-0.07	0.78
Latency	-0.27	0.25	-0.32	0.16	-0.41	7.22×10 <sup>-2</sup>	-0.07	0.78	-0.16	0.51	0.02	0.95	0.17	0.47
<b>Free-viewing task</b>														
Saccade amplitude (°/s)	0.10	0.66	0.10	0.66	0.00	0.99	0.06	0.81	0.14	0.55	-0.25	0.28	-0.18	0.45
Total eye blink frequency	0.07	0.77	0.05	0.85	0.25	0.28	0.19	0.42	0.11	0.64	-0.03	0.91	-0.14	0.57
<b>Smooth-pursuit task: Constant</b>														
Compensatory saccade frequency	0.44	5.55×10 <sup>-2</sup>	0.22	0.36	0.17	0.47	0.20	0.39	0.21	0.38	0.17	0.47	0.07	0.77
<b>Smooth-pursuit task: Sinusoidal</b>														
Compensatory saccade frequency	0.33	0.15	0.28	0.24	0.15	0.54	0.31	0.19	0.32	0.18	0.18	0.44	0.02	0.93

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining eye-movement measures are exploratory. saccades/s, saccades/second; °/s, degrees/second;  $\rho$ , Spearman's  $\rho$ ;  $p$ ,  $p$  value; cycles/s, cycles/second.

<sup>a</sup> For antisaccades.

<sup>b</sup> For predictive saccades.

<sup>c</sup> One-tailed (two-tailed for all other measures).

Table S4. Relationship between exploratory eye-movement measures and binocular rivalry rate for primary and exploratory stimulus conditions in healthy controls.

	Stationary green gratings		4 cycles/s green gratings		8 cycles/s green gratings		4 cycles/s anaglyph gratings		8 cycles/s anaglyph gratings		4 cycles/s anaglyph rings		8 cycles/s anaglyph rings	
	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$
<b>Antisaccade task</b>														
Latency <sup>a</sup>	0.02	0.95	-0.04	0.86	-0.11	0.64	0.09	0.72	-0.10	0.69	-0.09	0.71	0.07	0.77
Primary saccade gain <sup>a</sup>	-0.23	0.33	-0.27	0.25	-0.29	0.22	-0.27	0.24	-0.28	0.23	-0.32	0.17	-0.10	0.68
Final eye position gain <sup>a</sup>	-0.03	0.91	-0.01	0.97	0.16	0.51	-0.04	0.87	0.17	0.47	-0.06	0.79	-0.26	0.27
<b>Anticipatory task</b>														
% of predictive saccades	0.39	8.81×10 <sup>-2</sup>	0.41	7.24×10 <sup>-2</sup>	0.47	3.75×10 <sup>-2</sup>	0.24	0.31	0.31	0.18	0.17	0.48	0.23	0.34
Final eye position gain <sup>b</sup>	-0.10	0.69	-0.00	1.00	-0.25	0.32	-0.17	0.49	-0.39	0.12	0.03	0.92	0.17	0.49
<b>Self-paced task</b>														
Saccade rate (saccades/s) <sup>c</sup>	0.06	0.40	-0.04	0.44	-0.12	0.30	0.04	0.43	-0.04	0.43	0.08	0.36	0.25	0.14
<b>Prosaccade task</b>														
Primary saccade gain	-0.22	0.34	-0.35	0.13	-0.32	0.17	-0.16	0.51	-0.20	0.40	-0.27	0.25	-0.04	0.87
Final eye position gain	-0.38	0.10	-0.41	7.57×10 <sup>-2</sup>	-0.27	0.25	-0.27	0.25	-0.17	0.47	-0.46	4.35×10 <sup>-2</sup>	-0.42	6.24×10 <sup>-2</sup>
Latency	0.08	0.74	0.03	0.91	0.01	0.97	0.15	0.54	0.06	0.79	0.04	0.86	0.06	0.81
<b>Free-viewing task</b>														
Saccade amplitude (°/s)	0.01	0.99	-0.03	0.92	-0.04	0.88	0.10	0.69	0.07	0.78	0.01	0.96	-0.10	0.68
Total eye blink frequency	0.38	0.10	0.30	0.21	0.32	0.17	0.25	0.28	0.35	0.14	0.41	7.20×10 <sup>-2</sup>	0.25	0.28
<b>Smooth-pursuit task: Constant</b>														
Compensatory saccade frequency	-0.41	7.45×10 <sup>-2</sup>	-0.41	7.11×10 <sup>-2</sup>	-0.38	0.10	-0.49	2.99×10 <sup>-2</sup>	-0.43	6.04×10 <sup>-2</sup>	-0.33	0.16	-0.36	0.13
<b>Smooth-pursuit task: Sinusoidal</b>														
Compensatory saccade frequency	-0.39	8.83×10 <sup>-2</sup>	-0.46	4.27×10 <sup>-2</sup>	-0.43	6.04×10 <sup>-2</sup>	-0.43	5.94×10 <sup>-2</sup>	-0.41	7.57×10 <sup>-2</sup>	-0.20	0.39	-0.19	0.43

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining eye-movement measures are exploratory. saccades/s, saccades/second; °/s, degrees/second;  $\rho$ , Spearman's  $\rho$ ;  $p$ ,  $p$  value; cycles/s, cycles/second.

<sup>a</sup> For antisaccades.

<sup>b</sup> For predictive saccades.

<sup>c</sup> One-tailed (two-tailed for all other measures).



Table S5. Bayes factors for correlation coefficients between exploratory eye-movement measures and binocular rivalry rate for primary and exploratory stimulus conditions in bipolar disorder.

	Stationary green gratings	4 cycles/s green gratings	8 cycles/s green gratings	4 cycles/s anaglyph gratings	8 cycles/s anaglyph gratings	4 cycles/s anaglyph rings	8 cycles/s anaglyph rings
	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>
<b>Antisaccade task</b>							
Latency <sup>a</sup>	0.10	0.13	1.31 <sup>c</sup>	0.32	0.20	0.52 <sup>c</sup>	1.56 <sup>c</sup>
Primary saccade gain <sup>a</sup>	3.41	3.55	3.56	1.53 <sup>c</sup>	2.70 <sup>c</sup>	3.36	1.90 <sup>c</sup>
Final eye position gain <sup>a</sup>	3.29	3.39	3.45	3.22	3.54	2.04 <sup>c</sup>	2.74 <sup>c</sup>
<b>Anticipatory task</b>							
% of predictive saccades	0.73 <sup>c</sup>	2.32 <sup>c</sup>	2.68 <sup>c</sup>	2.70 <sup>c</sup>	2.79 <sup>c</sup>	0.46 <sup>c</sup>	0.44 <sup>c</sup>
Final eye position gain <sup>b</sup>	2.04 <sup>c</sup>	2.12 <sup>c</sup>	2.34 <sup>c</sup>	3.23	2.83 <sup>c</sup>	1.54 <sup>c</sup>	1.67 <sup>c</sup>
<b>Self-paced task</b>							
Saccade rate (saccades/s)	3.00 <sup>c</sup>	3.57	3.49	3.49	3.49	0.38 <sup>c</sup>	0.20
<b>Prosaccade task</b>							
Primary saccade gain	2.06 <sup>c</sup>	3.55	3.51	3.36	3.37	2.72 <sup>c</sup>	3.18
Final eye position gain	3.42	3.60	3.61	3.61	3.61	3.20	3.60
Latency	2.26 <sup>c</sup>	2.27 <sup>c</sup>	1.89 <sup>c</sup>	3.23	2.25 <sup>c</sup>	3.03	1.77 <sup>c</sup>
<b>Free-viewing task</b>							
Saccade amplitude (°/s)	3.37	3.50	3.36	3.60	3.61	1.29 <sup>c</sup>	1.26 <sup>c</sup>
Total eye blink frequency	1.49 <sup>c</sup>	3.02	0.66 <sup>c</sup>	3.54	3.03	3.60	2.72 <sup>c</sup>
<b>Smooth-pursuit task: Constant</b>							
Compensatory saccade frequency	3.06	3.51	3.61	3.57	3.60	3.61	3.01
<b>Smooth-pursuit task: Sinusoidal</b>							
Compensatory saccade frequency	3.58	3.44	3.61	3.25	3.38	3.61	2.79 <sup>c</sup>

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining eye-movement measures are exploratory. saccades/s, saccades/second; °/s, degrees/second; cycles/s, cycles/second; BF<sub>01</sub>, Bayes factors value for null hypothesis of there being no correlation.

<sup>a</sup> For antisaccades.

<sup>b</sup> For predictive saccades.

<sup>c</sup> More data (i.e., power) required to evaluate competing hypotheses.

Table S6. Bayes factors for correlation coefficients between exploratory eye-movement measures and binocular rivalry rate for primary and exploratory stimulus conditions in healthy controls.

	Stationary green gratings	4 cycles/s green gratings	8 cycles/s green gratings	4 cycles/s anaglyph gratings	8 cycles/s anaglyph gratings	4 cycles/s anaglyph rings	8 cycles/s anaglyph rings
	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>	BF <sub>01</sub>
<b>Antisaccade task</b>							
Latency <sup>a</sup>	3.22	2.42 <sup>c</sup>	3.00	3.18	2.42 <sup>c</sup>	2.45 <sup>c</sup>	3.61
Primary saccade gain <sup>a</sup>	3.32	3.03	3.42	2.77 <sup>c</sup>	2.93 <sup>c</sup>	2.29 <sup>c</sup>	3.47
Final eye position gain <sup>a</sup>	2.26 <sup>c</sup>	2.42 <sup>c</sup>	3.46	2.11 <sup>c</sup>	3.25	2.05 <sup>c</sup>	2.08 <sup>c</sup>
<b>Anticipatory task</b>							
% of predictive saccades	0.15	0.24	0.04	0.96 <sup>c</sup>	1.12 <sup>c</sup>	1.43 <sup>c</sup>	0.66 <sup>c</sup>
Final eye position gain <sup>b</sup>	2.28 <sup>c</sup>	1.20 <sup>c</sup>	3.27	1.39 <sup>c</sup>	2.96 <sup>c</sup>	1.88 <sup>c</sup>	1.67 <sup>c</sup>
<b>Self-paced task</b>							
Saccade rate (saccades/s)	3.05	3.27	3.61	3.24	3.56	3.55	2.92 <sup>c</sup>
<b>Prosaccade task</b>							
Primary saccade gain	1.69 <sup>c</sup>	1.83 <sup>c</sup>	0.29	2.99 <sup>c</sup>	2.60 <sup>c</sup>	1.47 <sup>c</sup>	1.64 <sup>c</sup>
Final eye position gain	1.17 <sup>c</sup>	1.95 <sup>c</sup>	0.35 <sup>c</sup>	2.91 <sup>c</sup>	3.32	0.76 <sup>c</sup>	0.51 <sup>c</sup>
Latency	3.50	3.53	3.29	3.16	3.60	3.61	3.46
<b>Free-viewing task</b>							
Saccade amplitude (°/s)	3.60	3.59	3.07	3.33	3.42	3.51	2.30 <sup>c</sup>
Total eye blink frequency	1.16 <sup>c</sup>	1.93 <sup>c</sup>	1.42 <sup>c</sup>	1.83 <sup>c</sup>	0.83 <sup>c</sup>	0.62 <sup>c</sup>	2.52 <sup>c</sup>
<b>Smooth-pursuit task: Constant</b>							
Compensatory saccade frequency	0.28	0.45 <sup>c</sup>	0.24	0.53 <sup>c</sup>	0.67 <sup>c</sup>	0.95 <sup>c</sup>	0.60 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>							
Compensatory saccade frequency	0.21	0.37 <sup>c</sup>	0.11	0.73 <sup>c</sup>	0.85 <sup>c</sup>	1.76 <sup>c</sup>	0.89 <sup>c</sup>

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining eye-movement measures are exploratory. saccades/s, saccades/second; °/s, degrees/second; cycles/s, cycles/second; BF<sub>01</sub>, Bayes factors value for null hypothesis of there being no correlation.

<sup>a</sup> For antisaccades.

<sup>b</sup> For predictive saccades.

<sup>c</sup> More data (i.e., power) required to evaluate competing hypotheses.

### Relationship between eye-movement measures and binocular rivalry rate using a less conservative alpha

The Bonferroni-adjusted  $\alpha$  used for the EM and BR rate correlations in the current study were more conservative than that used in our previous study (Law et al.<sup>6</sup>). That was because the current study assessed these correlations across a higher number of BR stimulus conditions. However, a number of EM and BR rate correlations were significant at a less conservative  $\alpha$  of 0.05. A pattern of significant moderate correlations was found between decreased maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task and slower BR rate for select stimulus conditions in controls ( $\rho=0.47-0.58$ ,  $p\leq 3.69\times 10^{-2}$ , two-tailed). For example, 8 cycles/s green and anaglyph gratings, and 4 cycles/s anaglyph rings (see Table 3 and Table S2). Other correlations observed were between prolonged antisaccade latency and slower BR rate across all primary stimulus conditions in BD ( $\rho=-0.48-0.64$ ,  $p\leq 3.17\times 10^{-2}$ , two-tailed; see Table S3). Further significant moderate correlations were found between various primary/exploratory EM measures and BR rate for select stimulus conditions in BD and controls ( $p\leq 4.44\times 10^{-2}$ ). Thus various EMs were found to be significantly associated with BR rate using a less conservative  $\alpha$  of 0.05.

### Group differences in age, hand and eye dominance, clinical state and psychometric measures

Demographic, clinical state and psychometric measures were compared between BD and controls to examine subject factors between these groups. The distribution of age, handedness, and eye dominance was not significantly different between BD and controls (independent-samples t-test and chi-square test of independence,  $p\geq 0.83$ ; see Table 1). STAI-trait was significantly higher in BD than in controls ( $p=1.77\times 10^{-4}$ ). Normality was violated for the distributions of STAI-state, MÅDRS, YMRS, subjective mood rating, and WTAR score (Shapiro-Wilk,  $p<0.05$ ), therefore non-parametric comparisons (Mann-Whitney U test,

Wilcoxon signed-rank test) were performed for these measures. STAI-state, MÅDRS, and YMRS ratings were significantly higher in BD than healthy controls for both the primary and subsequent (exploratory) testing sessions ( $p \leq 8.00 \times 10^{-3}$ ; see Table 1 and Table S7, respectively). Subjective mood rating was significantly lower in BD than healthy controls for both the primary and exploratory testing sessions ( $p \leq 3.04 \times 10^{-2}$ ). Baseline and post-test subjective mood rating was not significantly different for both the primary and exploratory testing sessions in BD ( $p \geq 0.14$ ), but was significantly lower in controls at post-test relative to baseline for the primary testing session ( $p = 9.75 \times 10^{-3}$ ). WTAR score was equivalently high between BD and controls ( $p = 5.96 \times 10^{-2}$ ). Thus clinical state, state-trait anxiety, and subjective mood were significantly different between the BD and healthy controls for both the primary and exploratory testing sessions.

Table S7. Psychometric data of overall sample for the exploratory testing session.

	Bipolar disorder (N=20)	Healthy controls (N=20)	<i>p</i>
<b>Formal state ratings, mean <math>\pm</math> SD / median <math>\pm</math> MAD</b>			
Total STAI-state	38.5 $\pm$ 13.5 / 41.2 $\pm$ 6	28 $\pm$ 6.9 / 29 $\pm$ 3.5	2.92 $\times 10^{-4}$ *
Total MÅDRS	10.5 $\pm$ 11.7 / 12.2 $\pm$ 9	0 $\pm$ 1.4 / 0.8 $\pm$ 0	3.90 $\times 10^{-5}$ *
Total YMRS	2 $\pm$ 5.5 / 4.5 $\pm$ 2	0 $\pm$ 0.7 / 0.4 $\pm$ 0	3.53 $\times 10^{-3}$ *
Subjective mood: baseline	6 $\pm$ 1.9 / 5.7 $\pm$ 1.5	8 $\pm$ 1.4 / 7.5 $\pm$ 1	1.96 $\times 10^{-3}$ *
Subjective mood: post-test	5 $\pm$ 2.1 / 5.5 $\pm$ 2	7 $\pm$ 1.2 / 6.9 $\pm$ 1	2.45 $\times 10^{-2}$ *

Note. *SD*: standard deviation. *MAD*: Median absolute deviation. STAI, State-Trait Anxiety Inventory; MÅDRS, Montgomery-Åsberg Depression Scale; YMRS, Young Mania Rating Scale. *p*, *p* value (Mann-Whitney U test; two-tailed).

## Relationship between eye-movement measures and clinical state, psychometric measures, age and medication

The association between each EM measure and demographic, clinical state, and psychometric measures was assessed in BD and controls, to examine whether there is a relationship between EMs and these subject factors. Non-parametric (Spearman's  $\rho$ ) correlation analyses were performed for the six primary EM measures and 13 exploratory EM measures to assess their association with age and each of the seven psychometric measures (i.e., STAI-trait, STAI-state, MÅDRS, YMRS, subjective mood rating at baseline and post-test, WTAR). *Tables S8* and *S9* show that primary EM measures were not significantly correlated with age or any psychometric measure in either the BD or control group ( $p \geq 1.01 \times 10^{-2}$ , two-tailed; Bonferroni-adjusted  $\alpha$ :  $0.05/48 = 1.04 \times 10^{-3}$ ), and similarly for the exploratory EM measures ( $p \geq 4.45 \times 10^{-3}$ , two-tailed; Bonferroni-adjusted  $\alpha$ :  $0.05/104 = 4.81 \times 10^{-4}$ ). For most correlations in both groups, corresponding Bayes factors indicate either weak evidence ( $1 < BF_{01} \leq 3$ ) or substantial evidence ( $3 < BF_{01} \leq 10$ ) in favor of the null hypothesis of no association between these measures, rather than the alternative hypothesis (i.e., that there was an association<sup>5</sup>), for primary EM measures (~98% for BD and ~83% for controls; see *Table S8*) and exploratory EM measures (~95% for BD and ~87% for controls; see *Table S9*). In particular, for saccade rate on the free-viewing task, there was either weak evidence ( $1 < BF_{01} \leq 3$ ) or substantial evidence ( $3 < BF_{01} \leq 10$ ) in favor of the null hypothesis of no association with age and any psychometric measure in either the BD or control group. Thus the observed lower free-viewing saccade rate in BD compared with the healthy group does not appear to be influenced by these subject factors. However, Bayes factors for some EM measures indicated substantial evidence ( $3 < BF_{10} \leq 10$ ) to strong evidence ( $10 < BF_{10} \leq 30$ ) for an association with various psychometric measures in BD and controls. These EM measures included predictive primary saccade gain, antisaccade latency, primary saccade gain and final eye

position on the prosaccade task, saccade amplitude and eyeblink frequency on the free-viewing task, compensatory saccade frequency on the constant and sinusoidal velocity smooth-pursuit tasks. For example, there was strong evidence ( $10 < \text{BF}_{10} \leq 30$ ) for an association between decreased maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task and higher WTAR score, and substantial evidence ( $3 < \text{BF}_{10} \leq 10$ ) for an association between decreased predictive primary saccade gain and higher MADRS rating (i.e., greater severity of depressive symptoms), though only in controls. These findings however, do not influence the key findings of the current study because according to frequentist and Bayesian statistics, there was: (i) no relationship between these particular EM measures and BR rate across the stimulus conditions; (ii) no group difference for these particular EM measures; or (iii) no group difference for these particular psychometric measures (reported in Law et al., in preparation). Across all primary and exploratory EM measures, no significant effect of medication type was found (Kruskal Wallis test;  $p \geq 6.19 \times 10^{-2}$ ), which indicates that medication type did not influence the key findings in the BD group. Although substantial evidence ( $3 < \text{BF}_{10} \leq 10$ ) was found for an association between prolonged prosaccade latency and age in BD and controls, all case-control pairs in the current study were age matched. Thus subject factors and medication type in BD do not appear to account for the observed low free-viewing saccade rate and relationship between EM measures and BR rate.

Table S8. Relationship between age, psychometric measures and eye-movement measures in bipolar disorder.

	Age			STAI-trait			STAI-state			MADRS			YMRS			Baseline mood			Post-test mood			WTAR		
	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>
<i>Primary measures</i>																								
<b>Free-viewing task</b>																								
Saccade rate (saccades/s)	-0.26	0.27	1.86 <sup>c</sup>	-0.03	0.91	3.58	-0.32	0.17	2.29 <sup>c</sup>	-0.05	0.84	3.59	-0.11	0.66	3.56	-0.03	0.91	3.58	-0.07	0.76	3.58	0.20	0.39	3.57
<b>Antisaccade task</b>																								
% of total step errors	0.00	0.99	3.61	-0.15	0.52	2.56 <sup>c</sup>	-0.22	0.34	2.98 <sup>c</sup>	-0.25	0.29	1.76 <sup>c</sup>	-0.11	0.65	3.34	-0.02	0.93	3.61	0.06	0.82	3.59	0.03	0.89	2.97 <sup>c</sup>
% of total gap errors	-0.02	0.93	3.61	-0.23	0.32	1.92 <sup>c</sup>	-0.31	0.19	2.07 <sup>c</sup>	-0.38	0.10	0.83 <sup>c</sup>	-0.15	0.52	3.11	0.22	0.34	3.08	0.09	0.72	3.61	-0.14	0.57	3.61
<b>Anticipatory task</b>																								
Predictive primary saccade gain <sup>a</sup>	-0.34	0.17	2.13 <sup>c</sup>	0.07	0.79	3.02	-0.08	0.76	2.58 <sup>c</sup>	0.21	0.40	2.52 <sup>c</sup>	0.05	0.84	3.11	-0.17	0.49	3.58	-0.08	0.76	2.96 <sup>c</sup>	-0.05	0.83	3.53
<b>Smooth-pursuit task: Constant</b>																								
Maintenance gain	0.17	0.47	2.96 <sup>c</sup>	0.11	0.65	1.63 <sup>c</sup>	-0.27	0.25	3.12	-0.05	0.82	3.14	-0.20	0.41	3.61	-0.12	0.60	1.41 <sup>c</sup>	-0.25	0.29	1.52 <sup>c</sup>	0.19	0.42	2.64 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>																								
Maintenance gain	0.42	0.07	1.11 <sup>c</sup>	0.25	0.30	3.25	0.43	0.06	2.15 <sup>c</sup>	0.16	0.50	3.61	0.32	0.18	1.67 <sup>c</sup>	0.23	0.34	1.71 <sup>c</sup>	0.25	0.29	2.67 <sup>c</sup>	0.30	0.21	3.06
<i>Exploratory measures</i>																								
<b>Antisaccade task</b>																								
Latency <sup>b</sup>	0.39	8.91×10 <sup>-2</sup>	1.31 <sup>c</sup>	0.21	0.39	2.37 <sup>c</sup>	0.35	0.13	1.13 <sup>c</sup>	-0.09	0.69	3.36	-0.11	0.65	3.47	0.27	0.24	2.92 <sup>c</sup>	-0.08	0.75	3.27	-0.08	0.73	3.28
Primary saccade gain <sup>b</sup>	-0.24	0.32	2.33 <sup>c</sup>	0.24	0.31	2.19 <sup>c</sup>	0.23	0.33	3.53	0.40	7.76×10 <sup>-2</sup>	0.40 <sup>c</sup>	0.11	0.63	2.45 <sup>c</sup>	-0.28	0.23	2.01 <sup>c</sup>	-0.02	0.95	3.30	0.27	0.25	2.67 <sup>c</sup>
Final eye position gain <sup>b</sup>	-0.36	0.12	1.13 <sup>c</sup>	-0.03	0.91	2.07 <sup>c</sup>	-0.21	0.38	1.33 <sup>c</sup>	0.12	0.62	2.32 <sup>c</sup>	0.25	0.29	2.83 <sup>c</sup>	-0.18	0.45	1.99 <sup>c</sup>	-0.21	0.38	3.60	0.35	0.13	3.60
<b>Anticipatory task</b>																								
% of predictive saccades	-0.10	0.68	3.48	-0.16	0.51	2.20 <sup>c</sup>	-0.26	0.28	1.48 <sup>c</sup>	0.05	0.83	3.61	-0.31	0.18	1.28 <sup>c</sup>	0.06	0.80	3.61	0.14	0.57	3.22	-0.28	0.23	1.94 <sup>c</sup>
Final eye position gain <sup>a</sup>	0.42	7.95×10 <sup>-2</sup>	2.68 <sup>c</sup>	-0.16	0.54	3.45	0.09	0.72	2.59 <sup>c</sup>	0.27	0.29	2.53 <sup>c</sup>	-0.09	0.71	3.41	-0.07	0.77	3.00	0.12	0.65	2.52 <sup>c</sup>	-0.28	0.27	2.69 <sup>c</sup>
<b>Self-paced task</b>																								
Saccade rate (saccades/s)	-0.09	0.71	3.37	-0.21	0.37	2.26 <sup>c</sup>	-0.27	0.25	2.65 <sup>c</sup>	-0.34	0.15	1.34 <sup>c</sup>	-0.11	0.64	3.24	-0.17	0.48	3.59	-0.28	0.24	3.34	0.17	0.48	2.54 <sup>c</sup>
<b>Prosaccade task</b>																								
Primary saccade gain	-0.17	0.47	2.46 <sup>c</sup>	0.02	0.95	3.61	-0.07	0.76	3.37	-0.08	0.75	3.61	-0.10	0.68	2.32 <sup>c</sup>	-0.03	0.92	3.50	-0.09	0.72	3.01	0.21	0.36	2.75 <sup>c</sup>
Final eye position gain	-0.08	0.73	3.50	0.20	0.40	2.54 <sup>c</sup>	0.16	0.51	2.10 <sup>c</sup>	0.16	0.51	1.74 <sup>c</sup>	0.11	0.64	1.60 <sup>c</sup>	-0.32	0.17	1.93 <sup>c</sup>	0.01	0.97	2.98 <sup>c</sup>	0.46	3.95×10 <sup>-2</sup>	2.00 <sup>c</sup>
Latency	0.61	4.45×10 <sup>-3</sup>	0.14	0.43	5.86×10 <sup>-2</sup>	0.65 <sup>c</sup>	0.51	2.12×10 <sup>-2</sup>	0.32	0.35	0.13	1.33 <sup>c</sup>	0.12	0.61	3.41	-0.22	0.35	2.45 <sup>c</sup>	-0.29	0.22	2.70 <sup>c</sup>	0.07	0.77	3.58
<b>Free-viewing task</b>																								
Saccade amplitude (°/s)	-0.27	0.24	2.47 <sup>c</sup>	-0.10	0.68	3.50	-0.21	0.37	3.26	-0.09	0.69	3.35	0.03	0.91	3.14	-0.27	0.25	3.43	-0.32	0.17	1.57 <sup>c</sup>	0.16	0.51	3.25
Total eye blink frequency	-0.01	0.98	2.63 <sup>c</sup>	-0.35	0.14	1.32 <sup>c</sup>	0.11	0.64	3.60	-0.33	0.16	1.68 <sup>c</sup>	-0.18	0.46	2.84 <sup>c</sup>	0.43	6.04×10 <sup>-2</sup>	1.43 <sup>c</sup>	0.53	1.68×10 <sup>-2</sup>	0.83 <sup>c</sup>	0.09	0.72	3.58
<b>Smooth-pursuit task: Constant</b>																								
Compensatory saccade frequency	0.10	0.66	2.17 <sup>c</sup>	0.01	0.98	3.54	0.05	0.85	1.61 <sup>c</sup>	0.14	0.57	3.56	0.05	0.83	3.59	-0.22	0.36	3.08	-0.08	0.72	3.13	-0.02	0.94	3.60
<b>Smooth-pursuit task: Sinusoidal</b>																								
Compensatory saccade frequency	0.22	0.35	1.96 <sup>c</sup>	0.03	0.90	3.02	0.02	0.92	1.23 <sup>c</sup>	0.04	0.87	3.34	0.08	0.74	3.48	-0.19	0.41	2.45	-0.16	0.50	2.23 <sup>c</sup>	0.10	0.67	3.32

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining eye-movement measures are exploratory. saccades/s, saccades/second; °/s, degrees/second;  $\rho$ , Spearman's  $\rho$ ;  $p$ ,  $p$  value (two-tailed); BF<sub>01</sub>: Bayes factors value for null hypothesis of there being no correlation; STAI, State-Trait Anxiety Inventory; MADRS, Montgomery-Åsberg Depression Scale; YMRS, Young Mania Rating Scale; WTAR: Wechsler Test of Adult Reading.

<sup>a</sup> For predictive saccades.

<sup>b</sup> For antisaccades.

<sup>c</sup> More data (i.e., power) required to evaluate competing hypotheses.

Table S9. Relationship between age, psychometric measures and eye-movement measures in healthy controls.

	Age			STAI-trait			STAI-state			MADRS			YMRS			Baseline mood			Post-test mood			WTAR		
	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$\rho$	$p$	BF <sub>01</sub>	$r$	$p$	BF <sub>01</sub>
<i>Primary measures</i>																								
<b>Free-viewing task</b>																								
Saccade rate (saccades/s)	0.02	0.94	3.61	-0.44	0.05	1.19 <sup>c</sup>	-0.33	0.16	2.37 <sup>c</sup>	-0.22	0.35	3.60	-0.23	0.32	1.93 <sup>c</sup>	0.10	0.68	3.24	0.12	0.60	3.61	0.06	0.79	2.20 <sup>c</sup>
<b>Antisaccade task</b>																								
% of total step errors	0.01	0.96	3.61	0.29	0.22	1.96 <sup>c</sup>	0.03	0.91	3.61	0.09	0.72	3.59	0.07	0.78	2.95 <sup>c</sup>	0.28	0.24	1.32 <sup>c</sup>	0.16	0.50	2.77 <sup>c</sup>	-0.11	0.63	3.10
% of total gap errors	-0.12	0.62	3.02	0.36	0.12	1.86 <sup>c</sup>	0.07	0.79	3.61	0.07	0.78	3.58	0.04	0.86	2.46 <sup>c</sup>	0.24	0.30	1.09 <sup>c</sup>	0.17	0.48	2.30 <sup>c</sup>	-0.10	0.67	3.10
<b>Anticipatory task</b>																								
Predictive primary saccade gain <sup>a</sup>	0.29	0.26	0.98 <sup>c</sup>	-0.24	0.36	1.66 <sup>c</sup>	-0.44	8.04×10 <sup>-2</sup>	0.90 <sup>c</sup>	-0.60	1.15×10 <sup>-2</sup>	0.29	0.02	0.93	3.58	0.26	0.32	1.32 <sup>c</sup>	0.23	0.37	0.93 <sup>c</sup>	0.29	0.27	2.51 <sup>c</sup>
<b>Smooth-pursuit task: Constant</b>																								
Maintenance gain	0.56	1.01×10 <sup>-2</sup>	0.73 <sup>c</sup>	-0.39	9.25×10 <sup>-2</sup>	0.68 <sup>c</sup>	-0.13	0.58	2.73 <sup>c</sup>	-0.01	0.96	3.22	0.03	0.91	2.87 <sup>c</sup>	0.06	0.79	3.56	-0.21	0.37	2.93 <sup>c</sup>	-0.01	0.97	2.55 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>																								
Maintenance gain	-0.14	0.56	3.18	0.17	0.47	0.11	0.05	0.85	1.34 <sup>c</sup>	0.10	0.69	3.41	-0.41	7.48×10 <sup>-2</sup>	2.41 <sup>c</sup>	0.05	0.85	3.30	0.08	0.75	2.22 <sup>c</sup>	-0.26	0.27	0.06
<i>Exploratory measures</i>																								
<b>Antisaccade task</b>																								
Latency <sup>b</sup>	0.24	0.30	1.78 <sup>c</sup>	0.46	4.27×10 <sup>-2</sup>	0.60 <sup>c</sup>	0.33	0.15	1.82 <sup>c</sup>	-0.16	0.50	2.72 <sup>c</sup>	0.16	0.49	3.59	0.15	0.54	2.28 <sup>c</sup>	-0.00	1.00	3.39	-0.43	5.89×10 <sup>-2</sup>	0.27
Primary saccade gain <sup>b</sup>	0.09	0.71	3.38	-0.55	1.16×10 <sup>-2</sup>	1.64 <sup>c</sup>	-0.37	0.11	3.30	-0.06	0.81	3.60	-0.11	0.65	1.98 <sup>c</sup>	-0.10	0.69	1.53 <sup>c</sup>	0.02	0.95	3.28	0.18	0.46	2.95 <sup>c</sup>
Final eye position gain <sup>b</sup>	0.08	0.75	3.18	0.26	0.27	3.50	0.15	0.53	2.06 <sup>c</sup>	0.18	0.45	3.36	-0.41	7.65×10 <sup>-2</sup>	1.34 <sup>c</sup>	0.10	0.67	2.11 <sup>c</sup>	-0.06	0.81	3.17	-0.11	0.65	3.27
<b>Anticipatory task</b>																								
% of predictive saccades	-0.14	0.55	3.15	0.19	0.41	1.88 <sup>c</sup>	0.19	0.43	3.19	0.19	0.41	3.55	-0.05	0.83	3.26	0.02	0.92	3.27	0.12	0.62	1.77 <sup>c</sup>	0.36	0.12	3.31
Final eye position gain <sup>a</sup>	0.23	0.37	1.22 <sup>c</sup>	0.16	0.53	3.60	0.13	0.61	3.57	0.04	0.88	3.37	0.17	0.50	2.85 <sup>c</sup>	0.04	0.89	3.03	-0.09	0.72	3.29	-0.35	0.16	3.29
<b>Self-paced task</b>																								
Saccade rate (saccades/s)	-0.27	0.24	1.25 <sup>c</sup>	-0.15	0.53	2.70 <sup>c</sup>	-0.05	0.83	3.23	-0.19	0.42	3.54	-0.05	0.83	3.47	0.28	0.24	3.00	0.30	0.21	2.67 <sup>c</sup>	0.08	0.73	1.93 <sup>c</sup>
<b>Prosaccade task</b>																								
Primary saccade gain	-0.35	0.13	1.59 <sup>c</sup>	-0.16	0.52	0.41 <sup>c</sup>	-0.08	0.73	2.19 <sup>c</sup>	0.12	0.62	3.23	0.31	0.18	1.77 <sup>c</sup>	-0.01	0.98	3.61	0.09	0.72	3.56	0.50	2.59×10 <sup>-2</sup>	0.07
Final eye position gain	-0.10	0.66	1.19 <sup>c</sup>	-0.42	6.83×10 <sup>-2</sup>	0.34 <sup>c</sup>	-0.26	0.26	1.82 <sup>c</sup>	-0.00	0.99	3.54	-0.03	0.90	3.52	0.15	0.52	3.61	0.16	0.49	3.60	0.40	8.07×10 <sup>-2</sup>	0.17
Latency	0.49	2.86×10 <sup>-2</sup>	0.22	-0.01	0.97	3.47	-0.01	0.95	3.61	-0.18	0.45	2.39 <sup>c</sup>	-0.15	0.53	3.00 <sup>c</sup>	0.12	0.61	3.52	-0.01	0.96	3.61	-0.45	4.94×10 <sup>-2</sup>	0.61 <sup>c</sup>
<b>Free-viewing task</b>																								
Saccade amplitude (°/s)	-0.27	0.24	2.14 <sup>c</sup>	0.15	0.53	3.59	0.03	0.91	3.23	0.19	0.43	3.32	0.53	1.62×10 <sup>-2</sup>	0.27	-0.18	0.45	3.61	-0.10	0.68	3.52	0.23	0.32	1.65 <sup>c</sup>
Total eye blink frequency	-0.10	0.67	2.56 <sup>c</sup>	0.26	0.28	2.49 <sup>c</sup>	0.35	0.14	1.32 <sup>c</sup>	0.41	7.69×10 <sup>-2</sup>	0.17	0.15	0.52	3.13	-0.39	9.07×10 <sup>-2</sup>	0.72 <sup>c</sup>	-0.33	0.15	0.82 <sup>c</sup>	-0.09	0.70	3.39
<b>Smooth-pursuit task: Constant</b>																								
Compensatory saccade frequency	0.34	0.14	1.69 <sup>c</sup>	-0.56	1.03×10 <sup>-2</sup>	0.10	-0.38	0.10	1.49 <sup>c</sup>	-0.25	0.28	3.19	0.07	0.78	3.51	0.06	0.80	3.36	0.03	0.91	3.52	0.12	0.62	2.08 <sup>c</sup>
<b>Smooth-pursuit task: Sinusoidal</b>																								
Compensatory saccade frequency	0.24	0.31	3.36	-0.51	2.07×10 <sup>-2</sup>	0.07	-0.24	0.32	2.11 <sup>c</sup>	-0.14	0.57	3.54	0.10	0.69	3.28	0.16	0.50	3.27	0.15	0.54	3.59	0.03	0.91	1.15 <sup>c</sup>

Note. Primary eye-movement measures are free-viewing saccade rate, percentage of antisaccade errors, predictive primary saccade gain, and maintenance pursuit gain on the smooth-pursuit task. The remaining eye-movement measures are exploratory. saccades/s, saccades/second; °/s, degrees/second;  $\rho$ , Spearman's  $\rho$ ;  $p$ ,  $p$  value (two-tailed); BF<sub>01</sub>: Bayes factors value for null hypothesis of there being no correlation; STAI, State-Trait Anxiety Inventory; MADRS, Montgomery-Åsberg Depression Scale; YMRS, Young Mania Rating Scale; WTAR: Wechsler Test of Adult Reading.

<sup>a</sup> For predictive saccades.

<sup>b</sup> For antisaccades.

<sup>c</sup> More data (i.e., power) required to evaluate competing hypotheses.



## Supporting Information Discussion

The current study found (i) no significant relationship between any primary EM measure and BR rate for exploratory stimulus conditions, and (ii) no significant relationship between any exploratory EM measure and BR rate for both primary and exploratory stimulus conditions. Bayes factors supported an association between prolonged antisaccade latency and slower BR rate in the BD group. The latency of correct antisaccades is generally interpreted as a measure of processing efficiency. Nevertheless, it has yet to be determined whether prolonged antisaccade latency reflects an impaired volitional antisaccade generation process (i.e., a programming or response deficit)<sup>7,8,9</sup> or an impaired reflexive saccade inhibition process (i.e., that additional processing resources are required for suppressing a reflexive saccade before initiating an antisaccade),<sup>10-12</sup> or possibly both. Given mechanisms underlying BR rate and its genetic basis remain just as uncertain, and is the subject of ongoing investigation, it is not useful to speculate on potential causal mechanisms of the observed association between antisaccade latency and BR rate in BD. However, to reiterate the main purpose of the current study: asserting that slow BR rate in BD is due to prolonged antisaccade latency requires antisaccade latency to be anomalous in BD — but such EM anomaly in BD was not observed in the current study (consistent with Katsanis et al.<sup>13</sup>; though prolonged antisaccade latency has been reported in SCZ<sup>7,14-21</sup>). Thus the slow BR rate endophenotype for BD cannot be explained by processes underlying an individual's antisaccade latency.

The self-paced task was included to assess for possible timing mechanisms that may contribute to an individual's BR rate.<sup>22</sup> Bayes factors supported an association between self-paced saccade rate and BR rate, albeit for just one stimulus type (8 cycles/s anaglyph rings). This finding however was in a direction opposite to that which would be expected, i.e., that slower BR rate in BD was found to be associated with higher self-paced saccade rate (rather than lower self-paced saccade rate). Moreover, to reiterate the main purpose of the current

study: this finding only pertained to one stimulus type and the current study found normal self-paced saccade rate in the BD group (i.e., no significant difference with controls). Thus the slow BR rate endophenotype for BD also cannot be explained by timing processes underlying an individual's self-paced saccade rate.

The EM measures that were associated with BR rate in the healthy group according to Bayes factors include percentage of predictive saccades, primary saccade gain on the prosaccade task, maintenance pursuit gain on the sinusoidal velocity smooth-pursuit task, frequency of compensatory saccades on the sinusoidal, and constant velocity smooth-pursuit tasks, though only for select stimulus conditions. These findings however conflict with those for the same measures in our previous study (Law et al.<sup>6</sup>), where there was double the number of healthy individuals compared to the current study. It is not clear what could explain the discrepant findings on these particular measures in the current study. Moreover, with respect to the main purpose of the current study, to assert that these EMs account for the finding of slow BR rate in BD requires these particular EMs to be anomalous in BD, but the current study found no difference between BD and healthy controls in these EMs. In addition, the current study's finding of normal prosaccade latency and gain in BD is consistent with the existing literature.<sup>23</sup>

Finally, the current study found no significant correlation between any of the primary and exploratory EM measures with the psychometric measures in BD and healthy groups. Bayes factors supported this null hypothesis for most of these associations. In particular, there was no relationship between an individual's free-viewing saccade rate and any psychometric measure in both the BD and healthy groups. Thus the observed lower free-viewing saccade rate in BD compared with the healthy group cannot be explained by these subject factors. There was however support for a relationship between other EM measures and psychometric measures in BD and healthy controls, but these findings were not

consistent across both groups, and there was also support for no group difference in those EMs. For example, prolonged prosaccade latency was found to be associated with greater state anxiety according to Bayes factors, though only in BD, and state anxiety was significantly higher in BD than healthy controls. However, the current study found normal prosaccade latency in BD. Thus there was no EM found to be abnormal in BD and could be explained by subject factors. Across both primary and exploratory EMs in BD, there was also no significant effect found for medication type. In addition, there was support for a relationship between prosaccade latency and age in both the BD and the healthy group. However, age was not a confounding variable for primary and exploratory EMs in both groups, because all case-control pairs were age-matched. With respect to the proposal that slow BR rate is an endophenotype for BD, the current study supports this endophenotype proposal by showing it is not explained by anomalous EMs in BD subjects.

### **Supporting Information References**

1. Snaith RP, Harrop FM, Newby DA. Grade scores of the Montgomery-Åsberg depression and the clinical anxiety scales. *Brit J Psychiat.* 1986;148:599–601.
2. McElroy SL, Martens BE, Winstanley EL, Creech R, Malhotra S, Keck PEJ. Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. *J Affect Disorders.* 2010;124:157–63.
3. Law PCF, Paton BK, Thomson RH, Liu GB, Miller SM, Ngo TT. Dichoptic viewing methods for binocular rivalry research: Prospects for large-scale clinical and genetic studies. *Twin Res Hum Genet.* 2013;16:1033–78.

4. Faul F, Erfelder E. *GPower: A priori-, post hoc-, and compromise power analyses for MS-DOS*. Bonn, Germany: Bonn University; 1992.
5. Jeffreys H. *The Theory of Probability* 3rd ed. Oxford, UK: Oxford University Press; 1961.
6. Law PCF, Paton BK, Riddiford JA, Gurvich CT, Ngo TT, Miller SM. No relationship between binocular rivalry rate and eye-movement profiles in healthy individuals: A Bayes factor analysis. *Perception*. 2015;44:643–61.
7. Klein C, Heinks T, Andresen B, Berg P, Mortiz S. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. *Biol Psychiat*. 2000;47:978–90.
8. Reuter B, Kathmann N. Using saccade tasks as a tool to analyze executive dysfunctions in schizophrenia. *Acta Psychol*. 2004;115:255–69.
9. Reuter B, Rakusan L, Kathmann N. Poor antisaccade performance in schizophrenia: An inhibition deficit? *Psychiat Res*. 2005;135:1–10.
10. Munoz DP, Everling S. Look away: The anti-saccade task and the voluntary control of eye movement. *Nat Rev Neurosci*. 2004;5:218–28.
11. Olk B, Kingstone A. Why are antisaccades slower than prosaccades? A novel finding using a new paradigm. *Neuroreport*. 2003;14:151–5.
12. Pratt J, Trottier L. Pro-saccades and anti-saccades to onset and offset targets. *Vision Res*. 2005;45:765–74.
13. Katsanis J, Kortenkamp S, Iacono WG, Grove WM. Antisaccade performance in patients with schizophrenia and affective disorder. *J Abnorm Psychol*. 1997;106:468–72.

14. Fukushima J, Fukushima K, Morita N, Yamashita I. Further analysis of the control of voluntary saccadic eye movements in schizophrenic patients. *Biol Psychiat*. 1990;28:943–58.
15. Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I. Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. *J Psychiat Res*. 1990;24:9–24.
16. Haraldsson HM, Ettinger U, Magnusdottir BB, Sigmundsson T, Sigurdsson E, Petursson H. Eye movement deficits in schizophrenia. *Eur Arch Psy Clin N*. 2008;258:373–83.
17. Harris MSH, Reilly JL, Thase ME, Keshavan MS, Sweeney JA. Response suppression deficits in treatment-naïve first-episode patients with schizophrenia, psychotic bipolar disorder and psychotic major depression. *Psychiat Res*. 2009;170:150–6.
18. Karoumi B, Saoud M, d’Amato T, Rosenfeld F, Denise P, Gutknecht C, et al. Poor performance in smooth pursuit and antisaccadic eye-movement tasks in healthy siblings of patients with schizophrenia. *Psychiat Res*. 2001;101:209–19.
19. Karoumi B, Ventre-Dominey J, Vighetto A, Dalery J, d’Amato T. Saccadic eye movements in schizophrenic patients. *Psychiat Res*. 1998;77:9–19.
20. Mazhari S, Price G, Dragović M, Waters FA, Clissa P, Jablensky A. Revisiting the suitability of antisaccade performance as an endophenotype in schizophrenia. *Brain Cognition*. 2011;77:223–30.
21. Nkam I, Thibaut F, Denise P, Van Der Elst A, Ségard L, Brazo P, et al. Saccadic and smooth-pursuit eye movements in deficit and non-deficit schizophrenia. *Schizophr Res*. 2001;48:145–53.

22. Pettigrew JD, Miller SM. A 'sticky' interhemispheric switch in bipolar disorder? *P Roy Soc Lond B Bio*. 1998;265:2141–8.
23. Harris MSH, Reilly JL, Thase ME, Keshavan MS, Sweeney JA. Response suppression deficits in treatment-naïve first-episode patients with schizophrenia, psychotic bipolar disorder and psychotic major depression. *Psychiat Res*. 2009;170:150–6.