DR. PHILLIP CHEUK FUNG LAW (Orcid ID : 0000-0002-4915-1999)

Article type : Original Article

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

Phillip C. F. Law^{1*}, Caroline T. Gurvich¹, Trung T. Ngo^{1,2†}, Steven M. Miller^{1,3†}

¹ Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred Hospital, Melbourne, Australia.

² Genetic Epidemiology Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Australia; Mater Research Institute-UQ, Neurosciences & Cognitive Health Program, Faculty of Medicine, University of Queensland, Brisbane, Australia.

³ School of Psychological Sciences, Monash University, Melbourne, Australia.

* Corresponding author:

Phillip C. F. Law, Level 4, 607 St Kilda Road, Melbourne, VIC 3004, Australia.

Email: phillip.law@monash.edu

† Miller and Ngo are co-senior authors

Word count: 4904

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/bdi.12515](https://doi.org/10.1111/bdi.12515)

This article is protected by copyright. All rights reserved

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.

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

Author Manuscript

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 fully understood.^{1–3} 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.^{4–13}

<Insert Figure 1 about here>

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).^{14,15} For example, in BD perceptual switches occur on average every 3 to 4 s (with some periods up to 7–10 s), compared with every 1 to 2 s in healthy individuals. The finding of slow BR rate in BD has since been independently replicated^{16–18} and notably, the historical literature reported corresponding evidence for switch rate of ambiguous figures (a different form of perceptual rivalry).^{19,20} Slow BR rate in BD also appears to be unaffected by either clinical state or medication^{14,17} (but see Jia et al.²¹ who report some effect of depressive state on BR rate; see also Zhu et al.¹⁸). These findings — together with demonstration that an individual's BR rate is approximately 50% genetically determined^{9,22} — supported the proposal that slow BR is an endophenotype for BD, suitable for use in large-scale genome-wide association studies (GWAS).^{11,23–25} Stimulus parameters for such studies are being optimized (Law et al., in preparation), and because thousands to tens of thousands of subjects are required for GWAS, an online platform of BR testing is being developed.²³ However, aspects of the slow BR trait require further investigation.²⁵

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.^{26–29} However, in BD (which has a shared genetic basis with SCZ)³⁰, EMs have not been extensively investigated and existing studies have reported inconsistent results.^{26,27,31} For example, BD has been associated with impaired maintenance pursuit gain,^{32–35} impaired predictive (primary) saccade gain,³⁶ and

increased antisaccade error,^{37–40} but these findings have not been replicated by other studies.^{41–43} 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.^{44–46} Despite this observation, the rate of BR is faster with real images than afterimages, suggesting saccadic EMs may indeed influence BR rate.^{44,45,47} In later studies of EMs recorded during BR viewing, saccadic EMs that induced retinal image shifts were shown to be associated with perceptual switches.^{48,49} In a recent study by Hancock et al.⁵⁰, 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.⁵¹, 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 study⁵¹ also extended the work of Hancock et al.⁵⁰ by assessing additional EM measures that had been used to show performance deficits in psychiatric groups (especially in BD and SCZ^{26–29,32,33,36–40,42,43,52}), and found no relationship between these EM measures and BR rate.

The study by Law et al.⁵¹ 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.

1. PATIENTS AND METHODS

1.1 Sample and clinical assessment

Twenty naïve clinically stable outpatients with BD (12 males; mean age=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.⁵³ All participants including healthy controls had their diagnostic status confirmed according to DSM-IV criteria with the Mini International Neuropsychiatric Interview (M.I.N.I.).⁵⁴ For healthy controls, medical and psychiatric history was screened using a brief questionnaire to exclude individuals with a psychiatric disorder (e.g., BD, SCZ, MDD), neurological disorder (e.g., epilepsy), brain injury, or visual disorders (e.g., strabismus, amblyopia, color vision deficiency). They were also screened to exclude those with first-degree relatives of individuals with a psychiatric disorder. For BD subjects, there was a similar medical screening and exclusion procedure, as well as screening with the M.I.N.I., 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 1.2). Trait anxiety and state anxiety was assessed with the State-Trait Anxiety Inventory (STAI)⁵⁵ and premorbid intelligence was estimated with the Wechsler Test of Adult Reading (WTAR).⁵⁶ Severity of depressive and manic symptoms was assessed with the Montgomery-Åsberg Depression Scale (MADRS)⁵⁷ and Young Mania Rating Scale (YMRS),⁵⁸ 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 Supplementary Results.

All subjects with BD were outpatients at the time of testing, with varying degrees of symptom severity rating on the MADRS and YMRS, ranging between 0–24 and 0–16, respectively (three subjects were moderate on the MADRS and two were moderate on the YMRS, based on the classifications of Snaith, Harrop, & Newby⁵⁹ and McElroy et al.⁶⁰). 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.

<Insert Table 1 about here>

1.2 Study protocol

Participants abstained from consuming caffeinated drinks, tobacco, and alcohol for 4 hours prior to testing given their known effects on BR rate^{7,61–64} and EMs.^{65–68} 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). Each subgroup was initially run on either the BR task or EM task, and initially viewed BR using either the green or anaglyph drifting grating stimulus conditions (see section 1.3). Therefore, each case-control pair completed all five primary BR stimulus conditions (see section 1.3) and all six EM tasks (see section 1.4), 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 Supplementary Methods and Results, and Law et al., in preparation).

1.3 Apparatus, protocol and analysis for binocular rivalry task

BR stimuli were generated with custom software programmed using Psychtoolbox-3^{69,70} in conjunction with MATLAB™ (MathWorks Inc., MA). 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/s. The luminance of all stimuli (mean=1.02 cd/m²) and the background (0.35 cd/m²) were measured using a LS-100 luminance meter 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/s green gratings; (iii) 8 cycles/s green gratings; (iv) 4 cycles/s red/blue gratings; and (v) 8 cycles/s red/blue gratings. Additional exploratory BR stimulus conditions are described in the Supplementary 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, mosaic image) or unusual percepts (e.g., filled circle, double images). BR testing was conducted in a quiet, dimly illuminated room. BR behavioral data collection was run with custom software generated in MATLAB™ (MathWorks Inc., MA) for Windows 7™ on a customized PC (see below).

After familiarizing subjects with the BR task, the BR testing session involved multiple 7-min blocks (see below), each comprising four 100-s trials. The blocks were separated by 110-s rest breaks and the trials 30-s rest breaks. The first few minutes of BR viewing have been characterized by increases in BR rate within individuals.^{4,13,71–76} However, BR rates stabilize with longer BR viewing periods,^{9,14} 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 account for potential order effects, stimulus type (green gratings and anaglyph gratings) and drift speed (4 and 8 cycles/s) were counterbalanced — with drift speed of each stimulus type grouped — across case-control pairs.

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). Block 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/s, 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" dual-screen LCD monitor (True3Di™; 60Hz frame rate, 1,280×1,024 resolution). Each screen was directly behind one of either 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 is transmitted through the half-silvered mirror while the adjacent image is reflected off the mirror, resulting in an interleaved (superimposed) stimulus of two orthogonally polarized images when naturally viewed.²³ 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 is 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" single-screen LCD monitor (Dell™ P2412H; 60Hz frame rate, 1,280×1,024 resolution) was used to simultaneously display the trial-based BR data collection protocol to the experimenter. Both monitors were connected to a customized PC (Dell™ Vostro 460 mini-tower; see Supplementary Methods).

All red/blue anaglyph BR stimuli were presented on a conventional 21.6" single-screen LCD monitor (Acer X213W; 60Hz frame rate, 1,920×1,080 resolution) connected to a laptop (HP Pavilion dv6-6138tx). 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 color 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 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.²³). To ensure BR viewing was not influenced by the effects of ghosting, subjects were instructed to (i) not tilt

or rotate their head, and (ii) view the rivalry stimulus through the center of the polarizer/monochrome filters.

Analysis of subjects' BR data employed custom software developed in MATLAB™ (MathWorks Inc., MA). 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. Statistical analyses were performed with PASW Statistics 17 and R (version 3.2.5).⁷⁷

1.4 Apparatus, protocol and analysis for eye-movement tasks

The apparatus and protocol for each of the EM tasks in the current study are identical to those used and fully detailed in Law et al.⁵¹. 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/m²) and background (0.16 cd/m²) was measured using a ColorCAL MKII Colorimeter. 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.⁵¹, the present experiment analyzed 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.'s⁵⁰ 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.⁵¹), 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, square-wave jerks) identified using the criteria detailed in Law et al.⁵¹. 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, $p \geq 0.46$). In addition to the measures detailed in Law et al.⁵¹, 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 are fully detailed in Law et al.⁵¹. 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 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 factors⁷⁸ 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 Supplementary Methods and Results.

2. RESULTS

2.1 Group comparisons of binocular rivalry rate

BR rate was compared between BD 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; $p < 0.05$), therefore multiple non-parametric (Mann-Whitney U test) comparisons were performed on BR rate between BD and controls for the five primary BR stimulus conditions. BR rate was significantly slower in BD than in controls across all the primary stimulus conditions ($p \leq 1.16 \times 10^{-3}$; Bonferroni-adjusted α : $0.05/5=0.01$), except stationary green gratings and 8 cycles/s 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 favor 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 (Law et al., in preparation).

2.2 Group comparisons of primary eye-movement measures

Having established that BR rate is slow in BD, the primary EM measures were compared between BD and controls. Normality was violated for the distributions of primary 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 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 α : $0.05/6 = 8.33 \times 10^{-3}$). The corresponding Bayes factors indicate weak evidence ($1 < BF_{01} \leq 3$) in favor 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 Supplementary Results, as are subjective mood and clinical state ratings (i.e., STAI-trait, STAI-state, MADRS, YMRS).

<Insert Table 2 about here>

2.3 Relationship between primary eye-movement measures and binocular rivalry rate

The association between each primary EM measure and BR rate was assessed in BD and controls, to examine whether there is a relationship between these EMs and slow BR rate in BD. Non-parametric (Spearman's ρ) 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 no significant correlation between any primary EM measure and BR rate across all primary stimulus conditions in BD and controls ($p \geq 7.87 \times 10^{-3}$; Bonferroni-adjusted α : $0.05/30 = 1.67 \times 10^{-3}$). In particular, saccade rate on the free-viewing task was not significantly correlated with BR rate in either the BD or control group ($p \geq 4.76 \times 10^{-2}$, one-tailed; see Figure 2). Table 3 also shows that for all correlations in BD and most correlations in controls (90%; including all correlations for free-viewing saccade rate), 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 primary EMs and BR rate, rather than the alternative hypothesis (i.e., that there was an association⁷⁹). There was however, substantial evidence ($3 < BF_{10} \leq 10$) 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/s green gratings; with decisive evidence for 8 cycles/s green gratings, i.e., $BF_{10} > 100$). 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 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 Supplementary Results, as are the non-significant findings regarding the relationship between primary/exploratory EM measures, psychometric assessment ratings and medication.

<Insert Table 3 about here>

<Insert Figure 2 about here>

3. 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, 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 BD or healthy groups. 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 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.

On 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^{37–40} (c.f. Fukushima et al.⁸⁰), deficits in predictive

primary saccade gain³⁶ (c.f. Crawford et al.⁴¹), and impaired maintenance pursuit gain^{32–35} (c.f. Lencer et al.⁴² and Moates et al.⁴³).

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 BD and healthy groups, Bayes factors did provide support for a group difference, suggesting 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.⁵⁰). The combination of results overall support 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.⁵⁰, 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 slow BR rate in BD and Bayes factors support for low free-viewing saccade rate in BD, along with reports in the literature of parietal cortex anomalies in BD.^{81,82} 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 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 Supplementary Results), the non-significant findings were verified with Bayes factors which overall supported the lack of association. Moreover, at less conservative α of 0.05, no significant correlation was observed for more than 95% of the correlational tests conducted between a primary EM measure and BR rate in BD and control groups (as reported in the Supplementary 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 due to chance alone. Nonetheless, greater statistical power might also reveal significant group differences with frequentist statistics, especially in 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 Supplementary 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)^{9,14–17} 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.²³ Development of this online approach, along with stimulus optimization studies (Law et al., 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 elusive¹¹, 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 trait¹⁵ — a model based on hemispheric activation asymmetries and now being reconsidered in light of neuroimaging findings of white matter callosal deficits in BD.^{83–85}

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 free-viewing saccade rate being lower in BD than healthy controls (albeit with no association between this measure and BR rate), and (ii) support for other EMs being normal in BD. 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.

ACKNOWLEDGEMENTS

We thank Lynette Millist for assistance with the smooth pursuit EM data analyses, Sam Brilleman for assistance with statistics, and all volunteers who participated in the study. CTG was supported by a National Health & Medical Research Council (NHMRC) Early Career Fellowship (ID 0546262). TTN was supported by NHMRC (ID 490976). SMM received support from NHMRC, the Defence Health Foundation, a 2012 NARSAD Young Investigator Grant (19163) from the Brain & Behavior Research Foundation (USA), and the Monash Institute of Medical Engineering.

DISCLOSURES

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

REFERENCES

1. Alais D, Blake R. *Binocular rivalry*. Cambridge, MA: MIT Press; 2005.
2. Blake R, Logothetis NK. Visual competition. *Nat Rev Neurosci*. 2002;3:13–21.
3. Miller SM, editor. *The constitution of visual consciousness: Lessons from binocular rivalry*. Amsterdam, The Netherlands: John Benjamins Publishing Company; 2013.
4. Aafjes M, Heuting JE, Visser P. Individual and interindividual differences in binocular retinal rivalry in man. *Psychophysiology*. 1966;3:18–22.
5. Breese BB. On inhibition. *Psychol Rev-Monogr S*. 1899;3:1–65.
6. Enoksson P. Binocular rivalry and monocular dominance studied with optokinetic nystagmus. *Acta Ophthalmol*. 1963;41:544–63.
7. George RW. The significance of the fluctuations experienced in observing ambiguous figures and in binocular rivalry. *J Gen Psychol*. 1936;15:39–61.
8. McDougall W. The physiological factors of the attention-process. *Mind*. 1903;12:473–88.
9. Miller SM, Hansell NK, Ngo TT, Liu GB, Pettigrew JD, Martin NG, et al. Genetic contribution to individual variation in binocular rivalry rate. *P Nat Acad Sci USA*. 2010;107:2664–8.
10. Mull HK, Armstrong G, Telfer B. The effect of brightness upon reversible perspectives and retinal rivalry. *A J Psychol*. 1956;69:123–5.
11. Ngo TT, Barsdell WN, Law PCF, Miller SM. *Binocular rivalry, brain stimulation and bipolar disorder*. In: Miller SM, editor. *The constitution of visual consciousness: Lessons*

from binocular rivalry. Amsterdam, The Netherlands: John Benjamins Publishing Company; 2013. p. 211–52.

12. Wade NJ, Ngo TT. *Early views on binocular rivalry*. In: Miller SM, editor. The constitution of visual consciousness: Lessons from binocular rivalry Amsterdam, The Netherlands: John Benjamins Publishing Company; 2013. p. 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, Liu GB, Mitchell PB, Ngo TT, et al. Slow binocular rivalry in bipolar disorder. *Psychol Med*. 2003;33:683–92.

15. Pettigrew JD, Miller SM. A ‘sticky’ interhemispheric switch in bipolar disorder? *P Roy Soc Lond B Bio*. 1998;265:2141–8.

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;11:539–46.

17. Vierck E, Porter RJ, Luty SE, Moor S, Crowe MT, Carter JD, et al. Further evidence for slow binocular rivalry rate as a trait marker for bipolar disorder. *Aust NZ J Psychiat*. 2013;47:371–9.

18. Zhu, R., Ye, X., Zhou, X., Yang, J., Yue, Y., & Wang, K. (2013). Application of binocular competition paradigm in patients with bipolar disorder. *Chinese Journal of Nervous and Mental Diseases*, 8, 449–452.

19. Ewen JH. The psychological estimation of the effects of certain drugs upon the syntonetic and schizophrenic psychoses: With a brief inquiry into a physiological basis of temperament. *J Ment Sci*. 1931;77:742–66.

20. Hunt JM, Guilford JP. Fluctuation of an ambiguous figure in dementia praecox and in manic depressive patients. *J Abnorm Soc Psych*. 1933;27:443–52.

21. Jia T, Ye X, Wei Q, Xie W, Cai C, Mu J, et al. Difference in the binocular rivalry rate between depressive episodes and remission. *Physiol Behav*. 2015;151:272–8.

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;16:1033–78.

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;68:371–90.
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, Matthysse 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;68:359–70.
30. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 2013;45:984–94.
31. Carvalho N, Laurent E, Noiret N, Chopard G, Haffen E, Bennabi D, 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, Bernstein IH, O'Neill HB, Cole D, et al. Smooth pursuit eye movement, prepulse inhibition, and auditory paired stimuli processing endophenotypes across the schizophrenia-bipolar disorder psychosis dimension. *Schizophr Bull.* 2014;40:642–52.
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;46:671–80.
34. Lencer R, Trillenberg K, Trillenberg-Krecker K, Junghanns K, Kordon A, Broocks A, et al. Smooth pursuit deficits in schizophrenia, affective disorder and obsessive-compulsive disorder. *Psychol Med.* 2004;34:451–60.
35. Trillenberg P, Sprenger A, Talamo S, Herold K, Helmchen C, Verleger R, et al. Visual and non-visual motion information processing during pursuit eye tracking in schizophrenia and bipolar disorder. *Eur Arch Psychiatry Clin Neurosci.* 2016:1–11.
36. Keedy SK, Bishop JR, Weiden PJ, Sweeney JA, Rosen C, Marvin R, et al. Disease and drug effects on internally-generated and externally-elicited responses in first episode schizophrenia and psychotic bipolar disorder. *Schizophr Res.* 2014;159:101–6.

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;170:150–6.
39. Tien AY, Ross DE, Pearlson G, Strauss ME. Eye movements and psychopathology in schizophrenia and bipolar disorder. *J Nerv Ment Dis.* 1996;184:331–8.
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;164:1900–6.
41. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L. Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. *Psychol Med.* 1995;25:461–71.
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;67:217–23.
43. Moates AF, Ivleva EI, O'Neill HB, Krishna N, Cullum CM, Thaker GK, et al. Predictive pursuit association with deficits in working memory in psychosis. *Biol Psychiat.* 2012;72:752–7.
44. Blake RR, Fox R, McIntyre C. Stochastic properties of stabilized-image binocular rivalry alternations. *J Exp Psychol.* 1971;88:327–32.
45. Wade NJ. Binocular rivalry between single lines viewed as real images and afterimages. *Percept Psychophys.* 1975;17:571–7.
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;15:227–32.
48. van Dam LCJ, van Ee R. The role of saccades in exerting voluntary control in perceptual and binocular rivalry. *Vision Res.* 2006;46:787–99.
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;6:1172–9.
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;44:643–61.
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, Amorim P, Janavs J, Weiller E, 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;134:382–9.
58. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. *Brit J Psychiat*. 1978;133:429–35.
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;124:157–63.
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 Ophth Vis Sci*. 1995;36:1548–54.
63. McDougall W, Smith M. *The effects of alcohol and some other drugs during normal and fatigued conditions*. London: HMS Office; 1920.
64. Sedorff HH. Effect of alcohol on the motor fusion reserves and stereopsis as well as on the tendency to nystagmus. *Acta Ophthalmol*. 1956;34:273–80.

65. Domino EF, Ni, L. S., Zhang H. Effects of tobacco smoking on human ocular smooth pursuit. *Clin Pharmacol Ther.* 1997;61:349–59.
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;17:283–92.
67. Thaker GK, Ellsberry R, Moran M, Lahti A, Tamminga C. Tobacco smoking increases square-wave jerks during pursuit eye movements. *Biol Psychiat.* 1991;29:82–8.
68. Wilkinson IMS, Kime R, Purnell M. Alcohol and human eye movement. *Brain Cogn.* 1974;97:785–92.
69. Brainard DH. The psychophysics toolbox. *Spat Vis.* 1997;10:433–6.
70. Pelli DG. The VideoToolbox software for visual psychophysics: Transforming numbers into movies. *Spat Vis.* 1997;10:437–42.
71. Cogan R, Goldstein AG. Reporting of fragmentations in the binocular rivalry of contours. *Am J Psychol.* 1972;85:569–84.
72. Goldstein AG. Retinal rivalry and Troxler's effect: A correlation. *Percept Psychophys.* 1968;4:261–3.
73. Hodges WF, Fox R. Effect of arousal and intelligence on binocular rivalry rate. *Percept Motor Skill.* 1965;20:71–5.
74. Hollins M. The effect of contrast on the completeness of binocular rivalry suppression. *Percept Psychophys.* 1980;27:550–6.
75. Suzuki S, Grabowecky M. Long-term speeding in perceptual switches mediated by attention-dependent plasticity in cortical visual processing. *Neuron.* 2007;56:741–53.
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 t tests for accepting and rejecting the null hypothesis. *Psychon B Rev.* 2009;16:225–37.
79. Jeffreys H. *The Theory of Probability* 3rd ed. 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;20:1626–30.
82. Lyoo IK, Sung YH, Dager SR, Friedman SD, Lee JY, Kim SJ, 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;71:362–64.
84. Sarrazin S, Poupon C, Linke J, Wessa M, Phillips M, Delavest M, et al. A multicenter tractography study of deep white matter tracts in bipolar I disorder: Psychotic features and interhemispheric disconnectivity. *JAMA Psychiatry*. 2014;71:388–96.
85. Miller SM. Vestibular neuromodulation: Stimulating the neural crossroads of psychiatric illness. *Bipolar Disord*. 2016;18:539–43.

TABLES

TABLE 1 Demographic, clinical and psychometric data for overall sample.

	Bipolar disorder (N=20)	Healthy controls (N=20)	<i>p</i>
Participants' characteristics			
Sex, male, <i>N</i> (%)	12 (60)	12 (60)	—
Age, years, mean $\pm$ <i>SD</i>	41.6 $\pm$ 13.4	41.6 $\pm$ 14.1	0.99 ^a
Right eye dominance, <i>N</i> (%)	13 (65)	13 (65)	1.00 ^b
Handedness, <i>N</i> (%)			0.83 ^b
Left	2 (10)	1 (5)	—
Right	16 (80)	17 (85)	—
Ambidextrous	2 (10)	2 (10)	—
History of psychotic features, <i>N</i> (%)	17 (85)	—	—
Formal state ratings, mean $\pm$ <i>SD</i> / median $\pm$ <i>MAD</i>^c			
Total STAI-state	38 $\pm$ 12.5 / 41.2 $\pm$ 9	29 $\pm$ 9.6 / 31.6 $\pm$ 6	8.00 $\times$ 10 ^{-3*}
Total MADRS	7 $\pm$ 7.5 / 8.5 $\pm$ 5.5	0 $\pm$ 1.3 / 0.8 $\pm$ 0	8.18 $\times$ 10 ^{-6*}
Total YMRS	4 $\pm$ 5.7 / 6 $\pm$ 4	0 $\pm$ 0.7 / 0.3 $\pm$ 0	3.36 $\times$ 10 ^{-5*}
Subjective mood: baseline	6 $\pm$ 1.7 / 6.1 $\pm$ 1	7.5 $\pm$ 1.2 / 7.6 $\pm$ 0.5	4.68 $\times$ 10 ^{-3*}
Subjective mood: post-test	5 $\pm$ 1.8 / 5.7 $\pm$ 1	7 $\pm$ 1.4 / 7 $\pm$ 1	3.04 $\times$ 10 ^{-2*}
Trait ratings, mean $\pm$ <i>SD</i> / median $\pm$ <i>MAD</i>			
Total STAI-trait	48 $\pm$ 9 / 48.8 $\pm$ 7	37 $\pm$ 6.8 / 38.5 $\pm$ 4	1.77 $\times$ 10 ^{-4 a,*}
Total WTAR	117 $\pm$ 10.2 / 114.6 $\pm$ 4	119 $\pm$ 3.5 / 119.9 $\pm$ 1.5	5.96 $\times$ 10 ^{-2 c}
Medication, <i>N</i> (%)			
No medication	3 (15)	—	—
Lithium only	1 (5)	—	—
Anticonvulsant only ^d	1 (5)	—	—
Atypical antipsychotics only ^e	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)	—	—

Note. All psychometric data collected in the exploratory testing session are reported in Supplementary Table S7. *SD*: standard deviation. *MAD*: Median absolute deviation. *p*: *p* value.

^aIndependent-samples *t*-test. ^bChi-squared test. ^cMann-Whitney *U* test. ^d benzodiazepine. ^e quetiapine, paliperidone, aripiprazole, olanzapine. **p*<0.05 versus healthy controls.

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

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

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 between-group difference was found (see Supplementary 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 Supplementary Table S1). In contrast, there was 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 group difference for the remaining exploratory EM measures according to Bayes factors. saccades/s: saccades/second. °/s: degrees/second. MAD: Median absolute deviation. *p*: *p* value (Mann-Whitney U test; two-tailed). BF₀₁: Bayes factors value for null hypothesis of there being no group difference.

^a For predictive saccades. ^b More data (i.e., power) required to evaluate competing hypotheses.

689 **TABLE 3** Relationship between primary eye-movement measures and binocular rivalry rate for the primary stimulus conditions in bipolar
690 disorder 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		
	ρ	p	BF ₀₁	ρ	p	BF ₀₁	ρ	p	BF ₀₁	ρ	p	BF ₀₁	ρ	p	BF ₀₁
<i>Bipolar disorder</i>															
Free-viewing task															
Saccade rate (saccades/s) ^a	0.07	0.38	3.57	0.38	4.76×10 ⁻²	1.32 ^c	0.03	0.46	2.64 ^c	0.19	0.21	2.48 ^c	0.31	9.42×10 ⁻²	1.66 ^c
Antisaccade task															
% of total step errors	0.02	0.93	3.17	0.12	0.63	2.63 ^c	-0.12	0.60	3.59	0.02	0.93	3.60	0.13	0.57	2.99 ^c
% of total gap errors	-0.04	0.87	2.97 ^c	0.06	0.80	2.62 ^c	-0.09	0.70	3.42	-0.13	0.58	3.40	0.06	0.82	3.17
Anticipatory task															
Predictive primary saccade gain ^b	0.26	0.30	2.78 ^c	-0.07	0.79	3.56	0.44	6.86×10 ⁻²	2.76 ^c	-0.10	0.70	3.03	0.03	0.91	3.59
Smooth-pursuit task: Constant															
Maintenance gain	-0.04	0.86	2.82 ^c	0.04	0.88	3.61	-0.35	0.13	2.77 ^c	0.07	0.78	3.55	0.15	0.53	3.60
Smooth-pursuit task: Sinusoidal															
Maintenance gain	-0.42	6.77×10 ⁻²	3.24	-0.05	0.85	3.58	-0.20	0.40	3.53	0.05	0.83	3.54	-0.07	0.77	3.61
<i>Healthy controls</i>															
Free-viewing task															
Saccade rate (saccades/s) ^a	-0.17	0.24	2.14 ^c	-0.30	0.10	1.36 ^c	-0.18	0.22	1.93 ^c	-0.18	0.22	2.16 ^c	-0.07	0.38	2.94 ^c
Antisaccade task															
% of total step errors	0.05	0.82	3.27	0.24	0.32	2.86 ^c	0.25	0.28	2.72 ^c	0.09	0.71	3.37	0.19	0.43	3.09
% of total gap errors	0.10	0.68	3.53	0.25	0.30	3.38	0.31	0.19	3.26	0.19	0.42	3.37	0.29	0.21	3.10
Anticipatory task															
Predictive primary saccade gain ^b	-0.11	0.67	3.61	-0.05	0.86	3.39	0.00	1.00	3.59	0.09	0.73	3.12	-0.05	0.86	3.59
Smooth-pursuit task: Constant															
Maintenance gain	-0.09	0.71	2.53 ^c	-0.17	0.47	2.88 ^c	-0.22	0.36	1.27 ^c	-0.08	0.73	3.58	-0.16	0.51	2.88 ^c
Smooth-pursuit task: Sinusoidal															
Maintenance gain	0.42	6.45×10 ⁻²	0.08	0.38	9.94×10 ⁻²	0.38 ^c	0.47	4.69×10 ⁻²	9.94×10 ⁻⁴	0.41	7.57×10 ⁻²	1.30 ^c	0.58	7.87×10 ⁻³	1.03 ^c

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. No significant correlation was found between the primary EM measures and binocular rivalry rate for any exploratory stimulus condition in either bipolar disorder or healthy controls (see Supplementary 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 or healthy controls (see Supplementary Tables S3 and S4). The corresponding Bayes factors indicated 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 for most correlations in both groups (see Supplementary Tables S5 and S6). saccades/s: saccades/second. cycles/s: cycles/second. ρ : Spearman's ρ . p : p value. BF_{01} : Bayes factors value for null hypothesis of there being no correlation.

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

FIGURES

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.

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

bdi_12515_f1.tif

bdi_12515_f2.tif

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Law, PCF;Gurvich, CT;Ngo, TT;Miller, SM

Title:

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

Date:

2017-09-01

Citation:

Law, P. C. F., Gurvich, C. T., Ngo, T. T. & Miller, S. M. (2017). Evidence that eye-movement profiles do not explain slow binocular rivalry rate in bipolar disorder: support for a perceptual endophenotype. *BIPOLAR DISORDERS*, 19 (6), pp.465-476. <https://doi.org/10.1111/bdi.12515>.

Persistent Link:

<http://hdl.handle.net/11343/293189>