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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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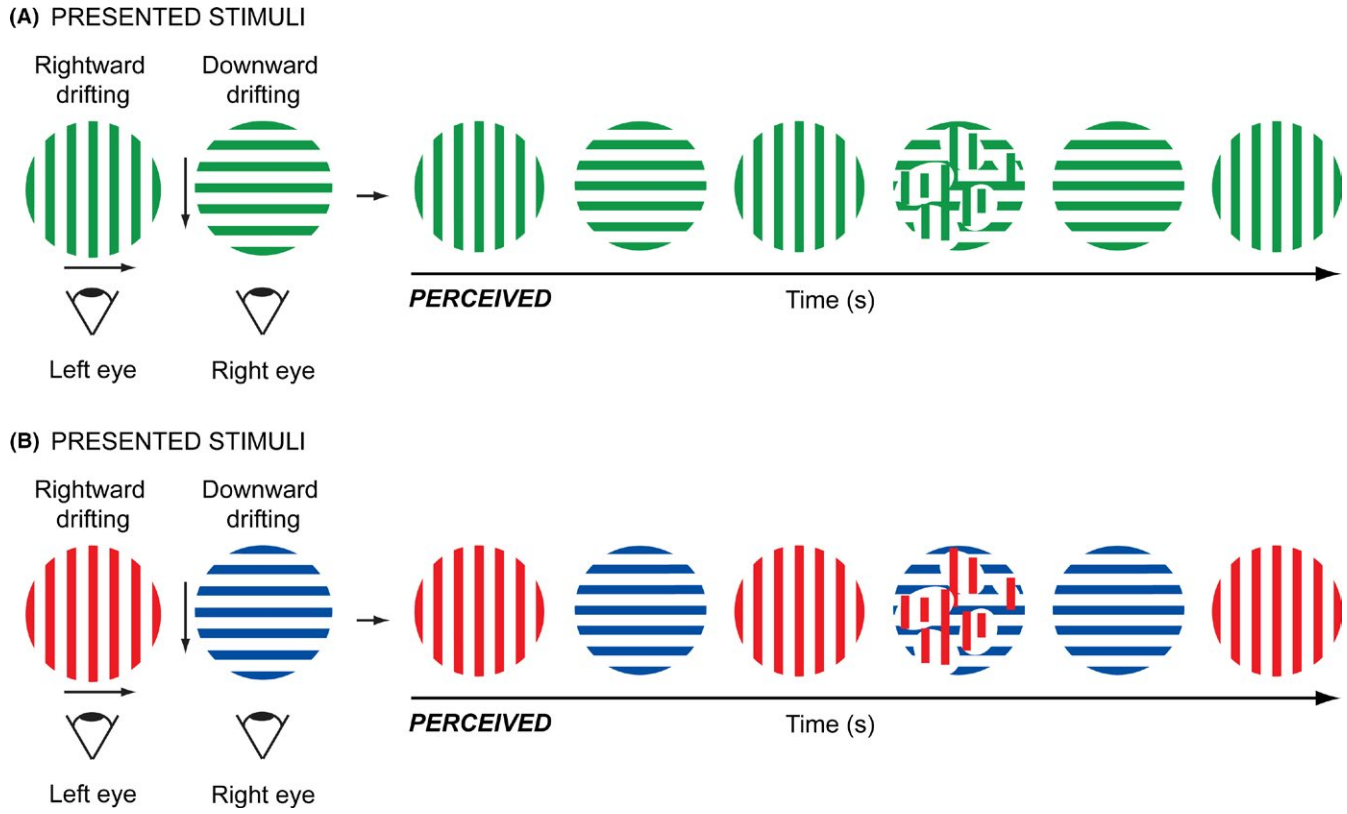

FIGURE 1 Binocular rivalry with (A) green gratings and (B) red/blue gratings. Presenting dissimilar images—such as rightward-drifting vertical gratings and downward-drifting horizontal gratings—simultaneously, one to each eye, causes each image to stochastically alternate in perception. Mixed percepts (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

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]

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 3-4 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[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 the 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 (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.[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 study[51] 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.

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.[53] All participants including healthy controls had their diagnostic status confirmed according to DSM-IV criteria with the Mini International Neuropsychiatric Interview (MINI).[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 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)[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 (MÅDRS)[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 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.[59] 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.

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[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 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[69,70] 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[a]
Right eye dominance, n (%)	13 (65)	13 (65)	1.00[b]
Handedness, n (%)			.83[b]
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[c]			
Total STAI-state	41.2±12.5/38±9	31.6±9.6/29±6	8.00×10^{-3}*
Total MÅDRS	8.5±7.5/7±5.5	0.8±1.3/0±0	8.18×10^{-6}*
Total YMRS	6±5.7/4±4	0.3±0.7/0±0	3.36×10^{-5}*
Subjective mood: baseline	6.1±1.7/6±1	7.6±1.2/7.5±0.5	4.68×10^{-3}*
Subjective mood: post-test	5.7±1.8/5±1	7±1.4/7±1	3.04×10^{-2}*
Trait ratings, mean±SD/median±MAD			
Total STAI-trait	48.8±9/48±7	38.5±6.8/37±4	$1.77\times10^{-4a,*}$
Total WTAR	114.6±10.2/117±4	119.9±3.5/119 ±1.5	5.96×10^{-2c}
Medication, n (%)			
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)	–	–

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

[a]Independent-samples *t* test.

[b]Chi-squared test.

[c]Mann–Whitney *U* test.

[d]Benzodiazepine.

[e]Quetiapine, paliperidone, aripiprazole and olanzapine.

*$P<.05$ vs healthy controls.

The luminance of all stimuli (mean=1.02 cd/m^2) and the background (0.35 cd/m^2) 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.[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 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.[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 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.[23]). 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).[77]

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.[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/m^2) and background (0.16 cd/m^2) 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.,[51] 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[50] 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, and square-save 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 ±2° and ±7° conditions in either BD or controls (Wilcoxon signed rank test, $P \geq .46$). 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 is 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 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[78] 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 ($P \leq 1.16\times10^{-3}$; Bonferroni-adjusted α: 0.05/5=0.01), except for stationary green gratings and 8 cycles/second anaglyph gratings ($P \geq 1.22\times10^{-2}$). 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 ($P \geq 1.32\times10^{-2}$; Bonferroni-adjusted α: $0.05/6=8.33\times10^{-3}$). 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 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 that there was no significant correlation between any primary EM measure and BR rate across all primary stimulus conditions in BD patients and controls ($P \geq 7.87\times10^{-3}$; Bonferroni-adjusted α: $0.05/30=1.67\times10^{-3}$). In particular, the saccade rate on the free-viewing task was not significantly correlated with BR rate in either the BD or control group ($P \geq 4.76\times10^{-2}$, 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	*P*	BF_{01}
Free-viewing task				
Saccade rate (saccades/second)	2.42±0.42	2.65±0.26	1.32×10^{-2}	0.19
Antisaccade task				
% of total step errors	21.53±11.11	18.06±10.42	0.24	1.83[b]
% of total gap errors	43.06±15.28	37.50±12.50	0.14	1.34[b]
Anticipatory task				
Predictive primary saccade gain[a]	0.73±1.05	0.96±0.64	0.35	2.52[b]
Smooth-pursuit task: constant				
Maintenance gain	0.95±0.03	0.98±0.03	8.10×10^{-2}	1.93[b]
Smooth-pursuit task: sinusoidal				
Maintenance gain	1.37±0.39	1.18±0.17	0.23	1.36[b]

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 ($1<BF_{10}\leq3$) for a group difference in compensatory saccade frequency on the constant velocity smooth-pursuit task (see Table S1). In contrast, there was weak evidence ($1<BF_{01}\leq3$) or substantial evidence ($3<BF_{01}\leq10$) 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_{01}, Bayes factor 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.

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[79]). There was, however, substantial evidence ($3<BF_{10}\leq10$) 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., $BF_{10}>100$). 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[37-40] (c.f. Fukushima et al.[80]), deficits in predictive primary saccade gain[36] (c.f. Crawford et al.[41]), and impaired maintenance pursuit gain[32-35] (c.f. Lencer et al.[42] and Moates et al.[43]).

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		
	ρ	*P*	BF_{01}	ρ	*P*	BF_{01}	ρ	*P*	BF_{01}	ρ	*P*	BF_{01}	ρ	*P*	BF_{01}
Bipolar disorder															
Free-viewing task															
Saccade rate (saccades/s)[a]	0.07	.38	3.57	0.38	4.76×10^{-2}	1.32[c]	0.03	.46	2.64 [c]	0.19	.21	2.48[c]	0.31	9.42×10^{-2}	1.66[c]
Antisaccade task															
% of total step errors	0.02	.93	3.17	0.12	.63	2.63[c]	−0.12	.60	3.59	0.02	.93	3.60	0.13	.57	2.99[c]
% of total gap errors	−0.04	.87	2.97[c]	0.06	.80	2.62[c]	−0.09	.70	3.42	−0.13	.58	3.40	0.06	.82	3.17
Anticipatory task															
Predictive primary saccade gain[b]	0.26	.30	2.78[c]	−0.07	.79	3.56	0.44	6.86×10^{-2}	2.76[c]	−0.10	.70	3.03	0.03	.91	3.59
Smooth-pursuit task: constant															
Maintenance gain	−0.04	.86	2.82[c]	0.04	.88	3.61	−0.35	.13	2.77[c]	0.07	.78	3.55	0.15	.53	3.60
Smooth-pursuit task: sinusoidal															
Maintenance gain	−0.42	6.77×10^{-2}	3.24	−0.05	.85	3.58	−0.20	.40	3.53	0.05	.83	3.54	−0.07	.77	3.61
Healthy controls															
Free-viewing task															
Saccade rate (saccades/s)[a]	−0.17	0.24	2.14[c]	−0.30	.10	1.36[c]	−0.18	.22	1.93 [c]	−0.18	.22	2.16[c]	−0.07	.38	2.94[c]
Antisaccade task															
% of total step errors	0.05	0.82	3.27	0.24	.32	2.86[c]	0.25	.28	2.72[c]	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	0.31	.19	3.26	0.19	.42	3.37	0.29	.21	3.10
Anticipatory task															
Predictive primary saccade gain[b]	−0.11	0.67	3.61	−0.05	.86	3.39	0.00	1.00	3.59	0.09	.73	3.12	−0.05	.86	3.59
Smooth-pursuit task: constant															
Maintenance gain	−0.09	0.71	2.53[c]	−0.17	.47	2.88[c]	−0.22	0.36	1.27 [c]	−0.08	.73	3.58	−0.16	.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]

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 ($1<BF_{01}\leq3$) or substantial evidence ($3<BF_{01}\leq10$) 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, cycles/second; saccades/s, saccades/second; ρ, Spearman's ρ; *P*, *P* value; BF_{01}, Bayes factor 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.

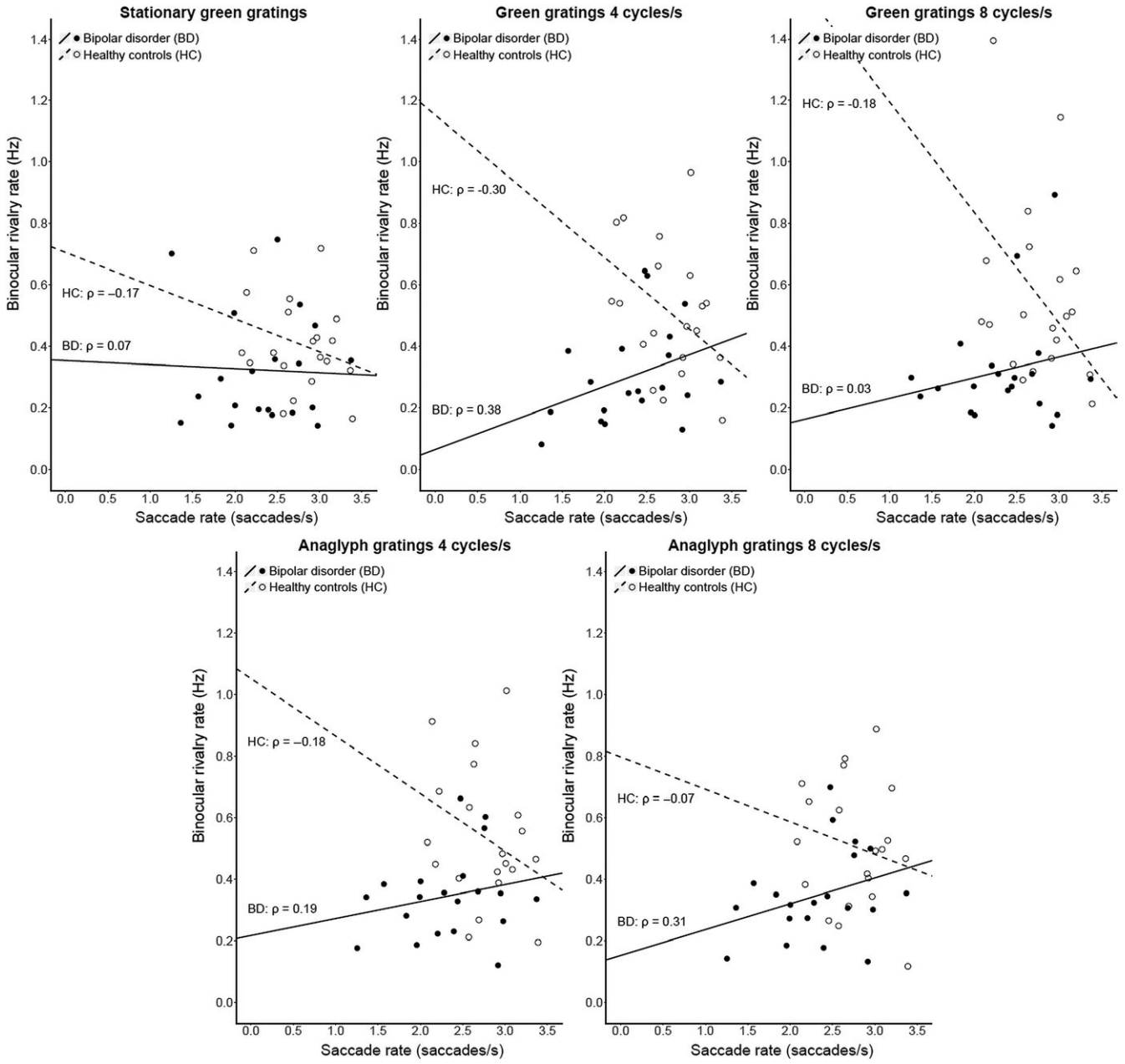

FIGURE 2 Scatterplots showing the association between an individual's saccade rate during free viewing of natural textures and their binocular rivalry rate for the five primary stimulus conditions. Binocular rivalry rate (Hz) is denoted along the *y*-axis and the saccade rate (saccades/second) along 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. ρ, Spearman's ρ

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.[50]). 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.,[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 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.[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 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 α 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)[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 (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,[11] 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[15]—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]

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

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

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