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Traits related to bipolar disorder are associated with an increased post-illumination pupil response

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ABSTRACT

Mood states in bipolar disorder appear to be closely linked to changes in sleep and circadian function. It has been suggested that hypersensitivity of the circadian system to light may be a trait vulnerability for bipolar disorder. Healthy persons with emotional-behavioural traits associated with bipolar disorder also appear to exhibit problems with circadian rhythms, which may be associated with individual differences in light sensitivity. This study investigated the melanopsin-driven post-illumination pupil response (PIPR) in relation to emotional-behavioural traits associated with bipolar disorder (measured with the General Behavior Inventory) in a non-clinical group ($n = 61$). An increased PIPR was associated with increased bipolar disorder-related traits. Specifically, the hypomania scale of the General Behavior Inventory was associated with an increased post-blue PIPR. Further, both the full hypomania and shortened '7 Up' scales were significantly predicted by PIPR, after age, sex and depressive traits were controlled. These findings suggest that increased sensitivity to light may be a risk factor for mood problems in the general population, and support the idea that hypersensitivity to light is a trait vulnerability for, rather than symptom of, bipolar disorder.

1. Introduction

Bipolar disorder (BD) is characterised by dysregulation across interacting systems of mood, circadian rhythms, the sleep/wake cycle, and reward. The disorder typically follows a remitting and relapsing lifetime course, with multiple periods of (hypo)mania and depression interspersed among periods of relative euthymia (American Psychiatric Association, 2013; Judd et al., 2003). Narrowly defined on the basis of diagnostic criteria, BD affects between 0.5 and 2.1% of the adult population, and defined using broader, spectrum-based criteria, between 2.4 and 4.4% of the adult population (Basso et al., 2013; Kessler et al., 2018). The cost of the disorder to the individual is substantial. Rates of divorce, substance use, health problems, occupational impairment, financial difficulty, and reckless, risk-taking behaviour are higher in persons with BD than the general population (Miller et al., 2014). The suicide rate in BD is 15 times that of the general population and it is thus among the most lethal of all psychological disorders (American Psychiatric Association, 2013). An understanding of the mechanisms that underpin vulnerability to the disorder is necessary to lessen individual and societal costs.

Sleep and circadian dysfunction are predictors of mood disturbance in both depressive and manic mood states in patients with BD. Manic or hypomanic episodes may be preceded by a reduction in sleep duration, while depressive episodes may be associated with either an increase or decrease in sleep need or duration (American Psychiatric Association, 2013; Goossens et al., 2010; Perlman et al., 2006; Sylvia et al., 2012). Discrete mood states in BD are additionally associated with changes in the timing of circadian rhythms (Harvey, 2011; Robillard et al., 2013; Wehr et al., 1980). Further, variation in several genes that are involved in circadian regulation (including *CLOCK* and *ADCY2*) have been found to convey increased risk for BD, pointing to a key role of circadian rhythms in the etiology of the disorder (Benedetti et al., 2003; Ikeda et al., 2018; Shi et al., 2008; Soria et al., 2010). Disruptions to circadian function are also commonly observed in people exhibiting neurobehavioral traits associated with BD, but whom have not yet developed a diagnosable condition. Large-scale studies have shown that higher levels of BD vulnerability traits are associated with greater instability in the 24-h rest-activity rhythm compared to those with lower vulnerability (Bullock and Murray, 2014; Lyall et al., 2018). Lower social rhythmicity, reflecting poor synchronisation of internal rhythms with the environment, has also been observed in people exhibiting higher levels of the BD vulnerability trait (Bullock et al., 2011), as has a

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tendency towards a preference for eveningness which is common in persons experiencing depressive symptoms (Chrobak et al., 2018; McGlashan et al., 2018b; Park et al., 2015).

Disruption of rhythms, such as that which has been observed in people with BD (or BD-related traits) may develop as a result of an abnormal response of the circadian system to light. The master circadian clock, the suprachiasmatic nucleus (SCN; Ralph et al., 1990), generates physiological rhythms of approximately 24 h and these are synchronised each day via light cues in the environment (Pittendrigh and Minis, 1964). An abnormally high or low response to these light cues can result in the disruption of circadian rhythms, or abnormal alignment of endogenous rhythms with behavioural patterns. This is shown notably in the circadian rhythm disorder Delayed Sleep-Wake Phase Disorder (DSWPD), whereby a chronically delayed clock appears to develop in part due to an increased circadian response to light (Aoki et al., 2001; McGlashan et al., 2018a; Watson et al., 2018). Patients with BD have also been shown to exhibit hypersensitivity to night time light (Hallam et al., 2009; Lewy et al., 1985), which may be associated with the onset of sleep and circadian disruption, and subsequent mood episodes in these patients. Further, mood stabilisers such as lithium and sodium valproate decrease the impact of light on the circadian clock (Hallam et al., 2005a, 2005b), indicating that the manipulation of light sensitivity may be an avenue for intervention in BD. Whether abnormal light sensitivity also underlies traits which may indicate vulnerability for the development of BD, in the absence of a diagnosable condition, is not well understood.

Intrinsically photosensitive retinal ganglion cells (ipRGCs) are a small collection of cells distributed across the inner layer of the retina which contain the photopigment melanopsin (Hattar et al., 2002). Melanopsin has a peak sensitivity to short-wave (blue) light (Bailes and Lucas, 2013), and ipRGCs have projections to a number of brain areas associated with non-visual light responses, including the master clock in the SCN (Fernandez et al., 2018; Gooley et al., 2003). IpRGCs therefore play a role in regulating the timing of the internal pacemaker, and may mediate other circadian responses including the suppression of melatonin, and the alerting and mood elevating effects of light. Melanopsin-containing ipRGCs are also responsible for the regulation of pupil dynamics, with their activation being associated with sustained constriction after light stimulus offset (Adhikari et al., 2015; Gooley et al., 2012). The melanopsin-driven post-illumination pupil response (PIPR) to bright blue light has been shown to be highly stable within individuals (ICC = .85), and across seasons (ICC = .83) even without mydriatics (Bruijel et al., 2016), therefore, the PIPR has recently gained interest as a marker of individual differences in circadian light sensitivity. The PIPR is related to individual differences in sleep timing, with increased melanopsin sensitivity being associated with later sleep timing (van der Meijden et al., 2016). Further, a decreased PIPR has been observed in patients with Seasonal Affective Disorder, which may contribute to circadian vulnerability in these patients (Roecklein et al., 2013). Melanopsin-driven pupil responses (e.g., PIPR) have not been studied in relation to either BD, or those who may exhibit trait vulnerability for the disorder. In the current study we investigated the association between BD-related emotional-behavioral traits and the PIPR. Based on evidence of increased melatonin suppression (a marker of circadian light sensitivity) in patients with BD (Hallam et al., 2009; Lewy et al., 1985; Nathan et al., 1999), and those at risk for BD (Nurnberger et al., 1988), we predicted that a larger PIPR would predict higher levels of BD-related traits.

2. Methods

All procedures were approved by the Monash University Human Research Ethics Committee (MUHREC). Participants gave written informed consent, and were reimbursed for their time. Data were collected between May and September 2018.

2.1. Participants

Sixty-one participants recruited from the community and a laboratory database completed the study. All participants were healthy, Caucasian adults aged between 18 and 34 years (M = 20.48, SD = 3.00), with 40 men and 21 women. Participants self-reported no current medical diagnoses or psychiatric conditions, and were not taking any medications at the time of the study. A small number (n = 4) of participants reported a lifetime history of depression or anxiety. Women were naturally cycling (free from hormonal contraceptives), and reported a regular menstrual cycle. Further, participants had not recently travelled across time-zones (2-week delay in participation per 2-h change in time zone, up to 3 months), or engaged in any shift-work. Lastly, participants were excluded if they were colour-blind (determined using the Ishiara' Test for Colour Deficiency).

2.2. Mood outcomes

The General Behavior Inventory (GBI; Depue et al., 1989) was used to indicate BD-related traits. The GBI is a self-report assessment tool designed to identify the presence, severity and fluctuation of lifetime hypomania/mania and depression related experiences. The GBI includes 73 items and is composed of three item sets that measure symptoms of depression, hypomania/mania, and mixed/biphasic symptoms. Factor analytic studies of the GBI have identified a two-factor solution, a hypomania/biphasic factor and a depression factor (Pendergast et al., 2015). Vulnerability to BD is therefore derived from a sum of scores on the biphasic and hypomanic items, forming the GBI-hypomania scale, while depression related experiences are measured using the GBI-depression scale. The short form of each of the GBI-depression and GBI-hypomania scales (7 Down and 7 Up respectively) were also calculated (Youngstrom et al., 2013). Participants completed the GBI in a private, quiet space.

2.3. Pupillometer

The PIPR was measured using a custom-built desk-mounted device (Monash Instrumentation Facility). The device consisted of a narrow-band light-emitting diode (LED; Cree) light source (see Table 1) that was presented to the right eye through diffusion glass (visual angle = 64°) during the light exposure protocol. The consensual pupil response of the left eye was recorded via infrared illumination (λ_{max} = 860 nm) with an infrared camera (Pixelink) and a telecentric lens (C-mount; Computar). A septum separated the light source and camera. The light source and camera were coordinated by custom software in MATLAB and a custom-built state-machine. A spectrometer was used to determine the wavelength, irradiance of the light stimuli, and the characteristics of each light stimuli can be found in Table 1 (UPRTek MK350N Spectrometer, Taiwan). A fixation point (dim red LED; Cree) was positioned at a distance of 4-meters from the participants' left eye to reduce accommodation and convergence during the recording.

2.4. Pupillometry protocol

The PIPR protocol comprised five consecutive 5-min blocks:

Table 1
Light characteristics for the red and blue light exposures.

	Light condition	
	Red	Blue
Photon Density (log photon flux log10 (1/cm^2/s)	15.20	15.17
Irradiance (μW/cm^2)	496.72	611.41
λpeak	635 nm	470 nm
Full-width half-maximum	20 nm	20 nm

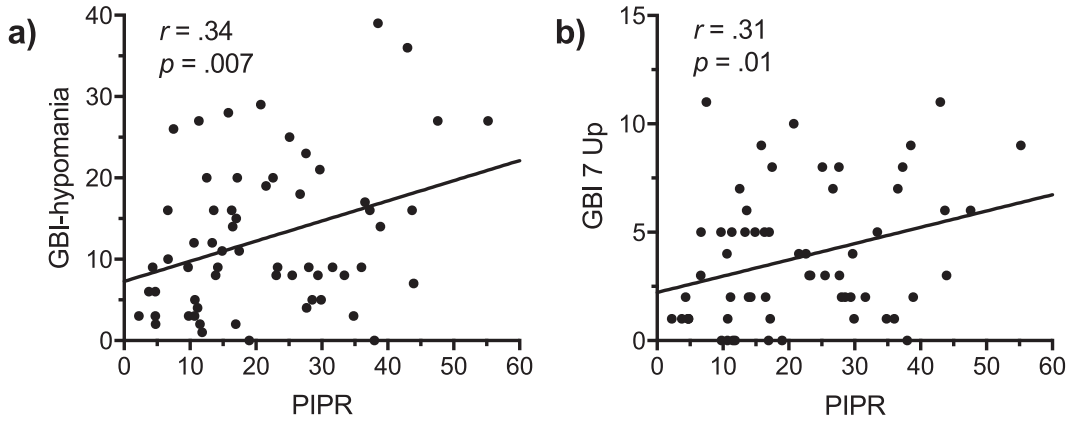

Fig. 1. Scatterplots demonstrating the relationship between a) relative PIPR % and GBI-hypomania scores and b) relative PIPR % and 7 Up scores.

baseline darkness (i.e., dark adaptation period); bright red light (λ_{max}: 635 nm); post-red darkness; bright blue light (λ_{max}: 465 nm); post-blue darkness, as reported in Bruijel et al. (2016). Bright red light was included in the protocol in order to maximise subsequent ipRGC activation to blue light, given the bi-stable nature of melanopsin (Mure et al., 2007). Participants sat upright with their head in a desk-mounted chin rest, and were asked to remain still during the protocol. The consensual response of the left pupil was recorded while light stimuli were delivered to the right eye. All assessments were conducted in the daytime hours (between 10 AM and 5 PM), as ipRGC driven pupil responses are stable during this period (Zele et al., 2011). Participants were instructed not to wear eye makeup, or contact lenses during the assessment.

2.5. Data analysis

2.5.1. Post-illumination pupil response measures

Prior to data analysis, eye blink and movement artefacts were removed and missing data was interpolated using the nearest neighbour method. Moreover, whereas pupil diameter was relatively stable during baseline darkness in most trials, some trials of post-blue darkness showed an initial dilation during the first minute before reverting to a sustained constriction, as reported elsewhere (van der Meijden et al., 2015). A similar observation was noted for the final minute of the post-blue block, whereby the pupil of some participants had already started dilating towards baseline size. This is due to the interaction between image forming photoreceptors (rods and cones) and ipRGCs during this time (Dacey et al., 2005; Gamlin et al., 2007). Therefore, the initial and last minute of each interval block were excluded from the analysis to reduce inter-assessment variation in pupil dynamics. Therefore, the averaged pupil diameter over the middle three minutes of each respective block was used to calculate the absolute, and relative PIPR % using the following formulae:

$$\begin{aligned}\text{Absolute PIPR (mm)} &= \text{baseline pupil diameter (mm)} \\ &\quad - \text{post blue pupil diameter (mm)}\,\text{Relative PIPR \%} \\ &= (\text{absolute PIPR mm/constriction during blue})*100\end{aligned}$$

Constriction during blue light was calculated as the difference between baseline pupil diameter, and the average pupil diameter during blue light.

2.5.2. Data cleaning

There were no univariate outliers identified in either PIPR mm or the relative PIPR % outcomes, and of the mood outcomes there was only one outlier identified on the 7 Down scale (z-score > 3.29). This individual was retained in the analyses. Two multivariate outliers were identified as exceeding the chi-square critical value for $df = 4$ (at $\alpha = .001$) of 18.47, 1 Female (age 34 years) and 1 Male (age 32 years), and were excluded from the hierarchical analysis. All other assumptions of multiple regression were appropriately satisfied. There were no missing values on any of the variables.

2.5.3. Statistical analyses

All statistical analyses were performed using IBM SPSS statistics version 21. The alpha level was set at .05 for all statistical analyses. Data distributions were moderately positively skewed for all PIPR and GBI variables, which is not unusual when measures of psychopathology are used in non-clinical populations, and particularly in samples of moderate size. A visual inspection of residual plots confirmed that the relationships amongst variables were generally linear and heteroscedastic. Therefore, raw data were used for all analyses. To assess the size and direction of the linear relationship between PIPR and GBI measures, bivariate Pearson's correlation coefficients (r) were calculated. Two hierarchical multiple regressions were conducted to determine the utility of the relative PIPR in predicting both the full GBI-hypomania scale, and the shortened 7 Up scale. In both cases, age and sex were controlled for at step one, before relative PIPR was entered at step two with the GBI-hypomania or 7 Up scale as the outcome variable. At step 3, the GBI-depression, and 7 Down scales were entered respectively, as these scales correlate significantly with the GBI-hypomania and 7 Up scales. The inclusion of these scales at step 3 allowed for estimation of the unique relationship between hypomanic/biphasic traits (either full scale or the 7-Up) and relative PIPR.

3. Results

The GBI-hypomania scale correlated positively and significantly with the relative PIPR %. GBI-depression did not correlate significantly with PIPR. In terms of participant characteristics, age did not significantly correlate with PIPR measures or the GBI, and these outcomes did not differ between the sexes (all $p > .05$). Table 2 displays descriptive data for the PIPR measures and mood outcomes, and their inter-correlations. Fig. 1 shows the relationships for the GBI-hypomania scale (Fig. 1a) and the 7 Up scale (Fig. 1b) with relative PIPR %. Fig. 2 demonstrates the change in pupil size across the 25-min protocol for two example participants, one with a high score on the GBI-hypomania scale, and one with a low score.

The results of the hierarchical multiple regressions are presented in Table 3 (full GBI scales) and Table 4 (7 Up and 7 Down scales). Table 3 shows that relative PIPR % added statistically significant explained variance to the regression model at Step 2, contributing 10% unique variance to the prediction of GBI-hypomania. In the final model, the relative PIPR % contributed significantly to the prediction of the GBI-hypomania scores, when depression was included in the model.

The same pattern of results was seen in the model using the 7 Up and 7 Down scales taken from the GBI, whereby relative PIPR %

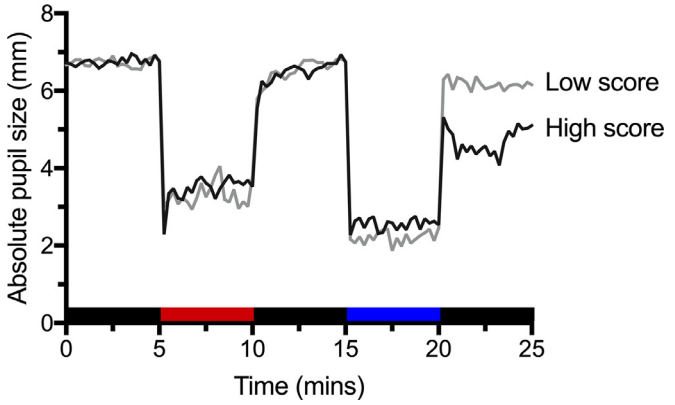

Fig. 2. Pupil size across the 25-min protocol for one example subject scoring high (score = 27) and one subject scoring low (score = 2) on the GBI-hypomania scale. Colour coding along the x-axis indicates the lighting condition of each 5-min period. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

predicted ~10% of the variance in 7 Up scores, and this remained significant after depression was included in the model (see Table 4).

4. Discussion

This study investigated the relationship between the PIPR and mood traits in a sample of healthy young adults. Our results show that, in a non-clinical group, emotional-behavioural traits related to BD are associated with increased melanopsin-driven PIPR. This indicates that even subthreshold disturbances in mood regulation are associated with altered circadian light signalling. Given previous findings that patients diagnosed with BD may exhibit increased circadian light sensitivity (e.g., Hallam et al., 2009; Lewy et al., 1985; Nathan et al., 1999), our finding that altered sensitivity is also associated with subthreshold symptoms supports the idea that increased light sensitivity may represent a vulnerability for mood disturbance.

Sleep, light, and mood are closely linked in BD. Sleep changes often precede the onset of mood episodes in these patients (Goossens et al., 2010; Sylvia et al., 2012), and the manipulation of light exposure and sleep can be an effective treatment for both manic and depressive episodes. Sleep deprivation and bright light therapy can be effective interventions for depressive episodes experienced as a part of BD (Leibenluft et al., 1995; Sit et al., 2007; Tseng et al., 2016). Further, dark therapy, or the deprivation of light during the night-time period, may alleviate symptoms of mania (Barbini et al., 2005). This therapy, or variations which use blue-blocking glasses to reduce blue-light exposure at night (Henriksen et al., 2014; Phelps, 2008) are thought to achieve a reduction in manic symptoms due to their ability to regulate circadian rhythms and sleep. Our finding of a relationship between the PIPR and mood experiences in a non-clinical group suggests that light processing may play a role in regulating mood in the general population as well as patient groups.

Previous work has demonstrated altered light sensitivity in patients with BD (Hallam et al., 2009; Lewy et al., 1985; Nathan et al., 1999) and seasonal affective disorder (Nathan et al., 1999; Thompson et al.,

Table 3
Prediction of GBI-hypomania scores by relative PIPR % and GBI-Depression: Hierarchical Regression controlling for age and sex.

	Variable	*B*	*SE B*	*β*	sr^2	R^2	ΔF	ΔR^2
Step 1	Age	−0.98	0.64	−.20	.04			
	Sex	0.88	2.59	.05	.00			
						.05	1.35	.05
Step 2	Age	−0.63	0.63	−.13	.02			
	Sex	0.76	2.46	.04	.00			
	Relative PIPR %	0.24	0.09	.33*	.10			
						.15	6.62*	.10
Step 3	Age	−0.39	0.34	−.08	.01			
	Sex	−0.88	1.33	−.05	.00			
	GBI-dep	0.47	0.04	.80**	.61			
	Relative PIPR %	0.14	0.05	.20**	.04			
						.74	136.18**	.61

Note. GBI-dep = GBI Depression subscale.
** $p < .01$;
* $p < .05$; $N = 59$.

Table 4
Prediction of 7 Up scores by PIPR and 7 Down scores: Hierarchical Regression controlling for age and sex.

	Variable	*B*	*SE B*	*β*	sr^2	R^2	ΔF	ΔR^2
Step 1	Age	−.11	.22	−.07	.00			
	Sex	.33	.87	.05	.00			
						.01	.23	.01
Step 2	Age	.01	.21	.01	.00			
	Sex	.29	.83	.05	.00			
	Relative PIPR %	.08	.03	.33*	.10			
						.11	6.47*	.10
Step 3	Age	−.02	.18	−.01	.00			
	Sex	.16	.69	.02	.00			
	7 Down	.61	.12	.54**	.29			
	Relative PIPR %	.07	.03	.29**	.08			
						.40	25.78**	.29

** $p < .01$;
* $p < .05$; $N = 59$.

Table 2
Means, standard deviations and correlations between PIPR and GBI outcomes.

	PIPR		General Behaviour Inventory				
	Baseline (mm)	Relative %	Total	GBI-hypomania	GBI-depression	7 Up	7 Down
PIPR							
Baseline (mm)	–	−.04	−.11	−.07	−.12	.07	−.13
Relative %		–	.21	.34**	.13	.31*	.01
GBI							
Total			–	.92**	.98**	.71**	.82**
GBI-hypomania				–	.81**	.84**	.60**
GBI-depression					–	.58**	.88**
7 Up						–	.39**
M	6.32	21.47	31.92	12.59	19.33	3.84	2.70
SD	0.76	12.72	25.29	9.22	17.24	3.07	3.26

Note: GBI = General Behaviour Inventory;
** $p < .01$;
* $p < .05$; $N = 61$

1990). Specifically, patients with BD have been shown to exhibit increased melatonin suppression to light relative to controls (Nathan et al., 1999). Similar outcomes have been shown in first-degree relatives of patients with BD (Nurnberger et al., 1988). Further, increased shifts in clock gene expression after exposure to bright light at night is associated with subthreshold symptoms related to BD (Cho et al., 2016). Melanopsin-driven pupil responses have not been studied in patients with BD, and therefore it is not known whether these abnormalities in non-visual light responses are due to altered functioning at the level of the retina, or at the level of the SCN. Our results suggest that these patients, and those with subthreshold levels of emotional-behavioral traits associated with BD may exhibit altered melanopsin sensitivity, although they may also reflect differences in function within the olivary pretectal nucleus (OPN). Altered melanopsin sensitivity has been shown to relate to differences in sleep timing (van der Meijden et al., 2016), and will likely have important impacts on the timing of circadian rhythms. Therefore, altered melanopsin signalling may be responsible for the changes to sleep and circadian function that precede the onset of mood episodes in patients with BD, and why light-related interventions are efficacious in this group.

An altered melanopsin-driven pupil response has also been observed in patients with seasonal affective disorder, where a reduction is seen relative to controls (Roecklein et al., 2013). This is in contrast to increased melatonin suppression findings in patients with seasonal affective disorder (Nathan et al., 1999; Thompson et al., 1990), or varied hyper- or hypo-sensitivity to light dependent on the season of measurement (Thompson et al., 1990). Although previous studies generally show increased melatonin suppression in patients with BD, some have found typical suppression levels in euthymic patients (Nurnberger et al., 2000; Whalley et al., 1991). It is therefore important to study melanopsin signalling, melatonin suppression, and potentially other markers of circadian light sensitivity together in a single study to determine the relative contribution of each to changes in circadian timing and function.

We previously demonstrated that a simple measure of the pupillary light reflex can differentiate between DSWPD patients with and without delayed circadian timing (McGlashan et al., 2018a). In that study, we showed increased pupil constriction velocity in the group of patients who exhibited a delay in circadian timing, but not those who exhibited the same symptoms in the absence of a delay in rhythms (groups originally characterised in Murray et al., 2017). Although this measure may be primarily driven by the activation of ipRGCs via rod and cone input, as opposed to direct melanopsin activation (Gooley et al., 2012), these findings indicate that abnormal retinal signalling may lead to different patterns of circadian synchronisation. Further, DSWPD patients with a circadian delay also show sustained pupil constriction after the offset of regular indoor lighting (Watson et al., 2018), and the phenotype with the highest sensitivity in our previous study (McGlashan et al., 2018a) also demonstrate higher levels of depression as a group (Murray et al., 2017). Patients with BD often experience comorbid circadian rhythm sleep-wake disorders (CRSWD), most commonly DSWPD (Takaesu et al., 2016). The presence of CRSWD is associated with a family history of suicide and younger age of onset in BD, and is predictive of mood episode relapse (Takaesu et al., 2016, 2018). The findings of the current study further strengthen the link between abnormal light signalling, circadian disruption, and mood disturbance.

It should be noted that while we found moderate associations between BD-related emotional-behavioural traits and increased PIPR, we did not study a clinical population. Further study will be required in patients with BD to determine whether the PIPR trait is relevant to the development of the diagnosable disorder. Additionally, it would be of interest to examine whether melanopsin-driven pupil responses have any predictive value. For example, if implemented in a group of young people with mood disturbance (depressive symptoms or episodes), it could be determined whether altered retinal signalling prospectively predicts the onset of manic episodes. Given that depressive episodes often precede manic or hypomanic episodes, and mania has a median age of onset of around 25 years (Berk et al., 2007; Kawa et al., 2005), a physiological marker of vulnerability to BD may assist in differentiating patients at a younger age to enhance treatment recommendations. This is of note, as first-line antidepressants such as selective serotonin reuptake inhibitors appear to enhance circadian light sensitivity (McGlashan et al., 2018c), an effect that would likely have negative consequences in a group already experiencing increased light sensitivity.

Consideration of neurobehavioral trait markers is a useful way to conceptualise the processes that underpin vulnerability to BD. The prominent model which underpins our conceptualisation of risk for BD suggests that vulnerability to the disorder exists along two correlated dimensions, characterised by depressive-like and hypomanic-like symptoms, respectively (Depue et al., 1989). This model is consistent with the correlated, but separable, genetic risk for depression and mania found in large-scale family (Merikangas et al., 2014) and twin studies (McGuffin et al., 2003). A neurobehavioural facilitation system, akin to the separable neurobiological approach/reward and inhibited withdrawal brain systems of Gray (1990) is thought to drive these vulnerability traits.

Animal studies have shown that ipRGCs are necessary for the mood altering effects of light (LeGates et al., 2012), and these cells have direct projections to the habenula (Fernandez et al., 2018), an area of the brain thought to be associated with reward regulation (for a review see Zhao et al., 2015). Patients with BD have reduced habenula volume (Savitz et al., 2011), and it was recently shown that light exposure suppresses activity in the human habenula (Kaiser et al., 2019). Therefore, altered melanopsin-related signalling as we observed in our study may play a role in regulating mood states in both healthy persons and patients with BD via impacts on the habenula. Given the mood-elevating effects of light (e.g., Meesters et al., 2011; Pail et al., 2011), increased melanopsin signalling may also lead to increases in light seeking behavior. Further study is needed to determine the specific nature of the retina-habenula pathway in humans, and the implications of this pathway for mood regulation in the general population and patients alike.

This study demonstrated an association between melanopsin-driven pupil responses, and emotional-behavioural traits related to BD in a non-clinical sample. Given the previous findings of increased circadian light sensitivity in BD, our findings in a population with subthreshold traits suggest that increased sensitivity may be a vulnerability for the development of BD and related mood outcomes. Distinct treatments are recommended for those experiencing BD as opposed to other mood disorders, so physiological markers of risk have the potential to improve outcomes for patients earlier in the treatment process, which is of significance given the large burden associated with mood disorders including bipolar disorder.

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Conflicts of interest

The authors report no relevant conflicts.

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