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Archival Report

Supersensitivity of Patients With Bipolar I Disorder to Light-Induced Phase Delay by Narrow Bandwidth Blue Light

Philipp Ritter, Bettina Soltmann, Cathrin Sauer, Abdulbaki Yakac, Lynn Boekstaegers, Mirjam Reichard, Konstanze Koenitz, Michael Bauer, Henry Güldner, Stefanie Neumann, Falk Wieland, and Debra J. Skene

ABSTRACT

BACKGROUND: Bipolar disorder is a severe chronic mental disorder. There is a bidirectional relationship between disease course and circadian phase. Significant circadian phase shifts occur during transitions between episodes, but episodes can also be elicited during euthymia by forced rapid changes in circadian phase. Although an instability of circadian phase has been described in multiple observational reports, no studies quantifying the propensity to phase shift following an experimental standardized stimulus have been published. This study therefore aimed to assess whether patients with bipolar I disorder (BDI) are more prone to phase delay following blue light exposure in the evening than healthy control subjects.

METHODS: Euthymic participants with BDI confirmed by Structured Clinical Interview for DSM-IV Axis I (n = 32) and healthy control subjects (n = 55) underwent a 3-day phase shift protocol involving exposure to a standardized dose of homogeneous, constant, narrow bandwidth blue light (478 nm, half bandwidth = 18 nm, photon flux = 1.29×10^{15} photons/cm^2/s) for 2 hours at 9:00 PM via a ganzfeld dome on day 2. On days 1 and 3, serial serum melatonin assessments during total darkness were performed to determine the dim light melatonin onset.

RESULTS: Significant differences in the light-induced phase shift between BDI and healthy control subjects were detected ($F_{1,82}$ = 4.110; p = .046), with patients with bipolar disorder exhibiting an enhanced phase delay (η^2 = 0.49). There were no significant associations between the magnitude of the phase shift and clinical parameters.

CONCLUSIONS: Supersensitivity of patients with BDI to light-induced phase delay may contribute to the observed phase instability and vulnerability to forced phase shifts associated with the disorder.

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Bipolar disorder is a severe and chronic mental disorder for which no comprehensive neurobiological etiologic model has yet been formulated. There is growing evidence linking the onset and course of the disease to an altered and less stable regulation of circadian rhythms. Delayed circadian timing (phase) appears to be common in bipolar disorder (1,2), and circadian phase shifts occur during transitions between episodes (3–5). An elevated propensity to phase shift may therefore be associated with the disorder.

Episodes of depression or mania are accompanied by considerable alterations in sleep-wake rhythms, and there is increasing evidence that sleep-wake regulation is altered interepisode (6) and before symptomatic onset (7,8). Moreover, both the timing of onset and the course of the disease appear to be strongly modulated by season. The emergence of episodes follows a seasonal pattern in a proportion of patients with bipolar disorder (9), and the age of onset of the disorder has repeatedly been shown to be inversely correlated with changes in illumination intensity (solar insolation) in springtime (10). The springtime peak for new episodes of mania (9) and the late autumn peak in depression coincide with rapid changes in day length (photoperiod) and resulting changes in the phase of biological rhythms. It is uncertain, however, whether the influence on circadian phase is the determining factor in the emergence of episodes. Other modes of forced phase shifts (advance or delay), such as those that occur after transmeridian travel, have been shown to increase the probability of ensuing mood episodes, with westbound travel (phase delay) more likely to precipitate depression and eastbound travel (phase advance) associated with mania (11). Clinical experience has also shown patients with bipolar disorder to be particularly sensitive to circadian misalignment resulting from shift work (12), and therapies that enforce reliable and constant lifestyle schedules with sufficient and regular sleep can reduce recurrence (13). A supersensitivity to the effects of evening/nighttime light exposure on melatonin synthesis in patients with bipolar disorder has been described in some (14–16) but not all (17,18) studies, and an increased propensity to phase delay has been found in subthreshold bipolarity (19). No studies on phase shifting have been conducted in people with a diagnosis of bipolar disorder.

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One chronobiological hypothesis of bipolar disorder posits that difficulties in maintaining cellular circadian rhythms may contribute to mood instability (20). Bipolar disorder is associated with variants in several Clock genes (21–23) and has been shown to be linked to more volatile circadian rhythms at the behavioral level (6). Lithium, the gold standard treatment for bipolar disorder, acts to stabilize cellular rhythms, possibly by increasing the amplitude of circadian gene expression (20,24,25).

Cellular clocks are synchronized via a light-entrainable clock located in the hypothalamic suprachiasmatic nucleus (SCN), which uses bright light in the blue wavelength range as its main time cue (zeitgeber) (26). Individual circadian phase, specifically the "time" of the internal SCN clock, can be reliably measured using the time of the evening dim light melatonin onset (DLMO) (27). Individual phase can be most efficiently manipulated experimentally (phase shift) by light stimulating the melanopsin-containing intrinsically photosensitive retinal ganglion cells. The effect size of this light-induced phase shift is dependent on the relative timing, intensity, spectral composition, and duration of the light (28–30) and correlates with the degree of melatonin suppression (30). Melanopsin hypersensitivity has been related to both phase delay (31) and hypomanic traits (32).

Neural networks with functional relevance in the generation and maintenance of affective states are tightly controlled by circadian pacemakers (33–37). Further indirect interactions between altered circadian mechanisms and mood have been demonstrated and involve immunologic, endocrine, and neurogenesis mechanisms (33). In humans, a length polymorphism of the *PER3* gene (*PER3* variable number tandem repeat [VNTR]) has been shown to influence both the acute response to light (melatonin suppression, increased alertness) and the course of bipolar disorder (38,39). Because manipulating the circadian system can directly influence affective states (40,41), it seems reasonable to propose that more fragile circadian functioning in the form of an increased propensity to phase shift may be implicated in the modulation or even pathogenesis of bipolar disorder.

We hypothesized that subjects with bipolar disorder would display a supersensitivity to the phase-delaying effects of blue light. The study aimed to determine whether patients with bipolar I disorder (BDI) exhibit a larger phase delay following a 2-hour evening exposure to narrow bandwidth blue light (478 nm; half bandwidth = 18 nm) compared with age- and sex-matched healthy control (HC) subjects. The correlation between the degree of phase shift with age, sex, *PER3* VNTR status, lithium treatment, and clinical characteristics was also assessed.

METHODS AND MATERIALS

Participants

The study was approved by the Institutional Review Board of the Medical Faculty of the Carl Gustav Carus University Hospital/TU Dresden (IRB00001473 and IORG0001076). Patients with BDI were recruited from the outpatient departments of four hospitals, as well as by advertisements in local newspapers and on websites of bipolar advocacy groups. HC subjects were recruited via noticeboards and advertisements in the local newspaper. After providing full informed consent, all participants were assessed using the German version of the Structured Clinical Interview for DSM-IV Axis I and Axis II interview (42) by an experienced psychiatrist. Mood was assessed using the Young Mania Rating Scale (43) and the 30-item Inventory of Depressive Symptoms (44). Ophthalmologic conditions were excluded by slit lamp examination and Snellen and Ishihara charts. In addition, body mass index, smoking status, current medication, family history of psychiatric disorder, and medical history were recorded. Further instruments used to characterize participants' sleep, chronotype/diurnal preference, seasonality, and general status of socioeconomic functioning were the Pittsburgh Sleep Quality Index (PSQI) (45), the Morningness-Eveningness Questionnaire (MEQ) (46), the Seasonal Pattern Assessment Questionnaire (SPAQ) (47), and the Global Assessment of Functioning (48).

HC participants were excluded if they or a first-degree relative had any Axis I psychiatric disorder. Further exclusion criteria for all participants included ophthalmologic conditions (excluding simple myopia/hyperopia); diagnosed sleep disorder; other disorders associated with impaired sleep (i.e., polyneuropathy); substance use disorder; inflammatory conditions; neurologic conditions; cancer; medical conditions deemed incompatible with study participation; use of melatonin, pregabaline, gabapentin, benzodiazepines, zopiclone, zolpidem, or β-blockers; recent transmeridian travel (within past 2 weeks); and shift or nighttime work within the past 3 months. All participants were required to be aged between 18 and 60 years and euthymic at the time of inclusion and on every assessment night (Young Mania Rating Scale < 5; 30-item Inventory of Depressive Symptoms < 8). The study was conducted during the winter months (November 2016–March 2017) to avoid the impact of summer evening light.

Assessments

Study participants attended the laboratory on 3 successive nights. All participants were required to adhere to a regular schedule of getting up no later than 7:30 AM, exposing themselves to outdoor light in the morning for >30 minutes, and switching lights off no later than midnight during 7 days before the first laboratory session. Adherence was ascertained by diary records, and participants who had substantially violated the protocol were rescheduled. On the day of assessment, participants were required not to consume food, alcohol, or caffeinated drinks after 1:00 PM.

On all three days of assessment (T1–T3), participants entered the laboratory at 6:00 PM. After clarifying the schedule, evaluating the diary, and establishing euthymia via the Young Mania Rating Scale and Inventory of Depressive Symptomatology-C_{30}, participants received a standard vegetarian meal of approximately 600 calories at 6:30 PM.

At 7:00 PM, all participants were seated in a reclining position under dim light conditions (≤10 lx, incandescent spectrum, in the direction of gaze) and allowed to listen to a standard audiobook via headphones (49). They were allowed to consume water or herbal tea but no food during the protocol.

After the meal, an 18G intravenous cannula was inserted into a forearm vein and blood collected for genetic analyses (*PER3* VNTR genotype) on day 1 (T1) only. On days 1 and 3 (T1+T3), at 7:30 PM, lights were turned off, and participants were exposed to complete darkness by applying a standard light-blocking eye

mask. Blood samples were taken every 45 minutes at 7:30, 8:15, 9:00, 9:45, 10:30, and 11:15 PM. The intravenous cannula was kept patent by 10-mL 0.9% NaCl solution. Patients were asked to rate their subjective sleepiness using the Karolinska Sleepiness Scale (50) before the blood sampling times. At 11:15 PM, participants were discharged.

On day 2 (T2), six Ag/AgCl electroencephalography electrodes (F3, C3, O1, Cz, A2, GND) and electrocardiography leads (RA, LL) were attached. Data capture was performed via a miniaturized recorder (electroencephalography and pupillometry data presented in separate publication). At 7:30 PM, lights were turned off and a standard light-blocking eye mask was applied until 8:55 PM.

Between 9:00 PM and 11:15 PM, participants were exposed to homogeneous and constant narrow bandwidth blue light (478 nm, half bandwidth = 18 nm, 1.29×10^{15} photons/cm^2/s) for 2 hours via a barium sulfate–coated ganzfeld dome (OptoPolymer) (for spectral distribution of the light, see Figure S1) while seated. Within the dome, light-emitting diodes and a true color sensor were mounted inside an aperture ring that enabled a highly uniform light distribution. The aperture ring had an inner diameter of 30 cm where participants placed their face on a chin and forehead rest.

An in-house light control system adjusted the brightness during light administration in the sphere, depending on the participant's pupil size (Figure S2). Pupillometry data were sampled at 30 Hz using a monochrome DMM 22BUC03 camera (The Imaging Source) and stored on a computer for analysis. Mean pupil size was transferred every 10 seconds via RS-232 serial bus to the microcontroller to control light-emitting diode light brightness. The microcontroller had an internal proportional-integral controller with a very low gain so brightness shifted smoothly to the new value (for a detailed description, see Figures S3 and S4). Participants were instructed not to shut their eyes and this was monitored by the pupillometry software, which gave a warning sound if pupils remained undetected for >10 seconds. Every 30 minutes, participants were allowed to remove their head from the dome, recline, and gaze ad libitum for 5 minutes (for irradiance measures, see Tables S1 and S2).

Laboratory Procedures

Blood was collected for melatonin analysis and genotyping. After standing for 30 minutes at room temperature and centrifugation at 1000*g* for 15 minutes at 4 °C, supernatant serum and EDTA whole blood were stored at –80 °C until further analysis.

Serum melatonin concentrations were measured in duplicate using a direct radioimmunoassay with ^{125}I-labeled melatonin according to the manufacturer's protocol (IBL-International). The limit of detection was 0.9 pg/mL, and the interassay coefficients of variation (CV%) were 12.81% at 10 pg/mL (n = 25) and 5.75% at 100 pg/mL (n = 25).

Genomic DNA was extracted from frozen (–80 °C) EDTA whole blood using QIAamp DNA Blood Mini kit (Qiagen) according to the manufacturer's protocol. To quantify and assess the purity of DNA, the absorbance at 260 nm and the ratio A260/280 and A260/230 was measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific).

For *PER3* genotyping, polymerase chain reaction was performed with the following primers: 5′-TGT CTT TTC ATG TGC CCT TAC TT-3′ and 5′-TGT CTG GCA TTG GAG TTT GA-3′ (51). The polymerase chain reaction was carried out in a 25-μL volume containing 150 ng DNA, 0.5 μM of each primer, 200 μM deoxynucleotide triphosphate, 1 × Q5 reaction buffer, and 0.02 U/μL Q5 high-fidelity DNA polymerase (New England Biolabs). After an initial step of 30 seconds at 98 °C, 30 cycles of amplification (10 s at 98 °C, 30 s at 65 °C, 25 s at 72 °C) and a final elongation step of 5 minutes at 72 °C were performed. An aliquot of polymerase chain reaction product was analyzed on agarose (2% agarose LE; Biozym Scientific GmbH) gel electrophoresis (5 V/cm for 90 min) to distinguish between the *PER3* VNTR 5 repeat allele (401 bp), the *PER3* 4 repeat allele (347 bp), and the heterozygotes (347 and 401 bp).

Statistical Analysis

Based on previous publications regarding light-induced melatonin suppression, which is assumed to be linearly related to phase shift (30) in patients with BDI (16), an increase in the magnitude of phase shift of ~40% in patients was anticipated. Based on a mean phase shift (SD) in HC subjects of 1.07 hours (0.36 hours) and in BDI of 1.50 hours (0.5 hours) for 1-β = 0.9, α = 5%, and the assumption of a sampling ratio of HC: BDI = 2, the minimum group size was calculated as HC = 24 and BDI = 12.

Phase shift was calculated as the DLMO between T1 and T3 using the established "hockey stick" method (52) (Figure S5). Individual circadian phase was calculated from DLMO at T1. Demographic, chronobehavioral, and clinical characteristics were compared using two-tailed unpaired t test and χ^2 tests as appropriate. Potential relevant confounders were included in the analysis as covariates. Groupwise comparisons were made following visual inspection of *Q-Q* plots and assessment of normal distribution using the Shapiro-Wilk test. Outliers were identified and removed using the outlier labeling rule with g = 1.5 (53). t tests and univariate analysis of covariance were used as appropriate to compare differences in outcomes between the BDI and HC groups. Group differences in phase shift were adjusted for DLMO at T1 to control for individual circadian phase. Effect sizes were calculated using eta squared (η^2) test.

Differences in distribution of *PER3* VNTR genotype between HC and BDI was calculated using χ^2 tests. The interaction of *PER3* with light-induced phase shift was calculated using the Kruskal-Wallis test.

The effect of mood-stabilizing medication was assessed using analysis of covariance comparing patients receiving the mood stabilizer lithium with those receiving other medication adjusted for DLMO at T1.

The relationship between the magnitude of phase shift and demographic and clinical characteristics (age, PSQI, MEQ, and Global Assessment of Functioning) for the total was evaluated using nonparametric partial correlation coefficients with DLMO at T1 and group as controlling variables.

Number of manic and depressive episodes and suicide attempts (summarized as disease course parameters) were adjusted for time at risk. Time at risk was calculated as time since age of onset in years. The relationship between the magnitude of phase shift and disease course for the BDI

sample was evaluated using nonparametric partial correlation coefficients with DLMO at T1 as controlling variable.

The interaction between seasonality (SPAQ) and phase shift was assessed using linear regressions adjusted for DLMO at T1.

Differences in pupil diameter between the study groups were assessed using *t* tests.

All analysis data are presented as mean ± SD.

RESULTS

A total of 105 participants were screened and enrolled into the study, with 87 participants completing the entire protocol. Reasons for dropout included 9 participants who withdrew without explanation, 3 were working shifts, 2 were currently depressed, 1 was actively consuming Δ^9-tetrahydrocannabinol/amphetamines, 2 could not tolerate blood sampling during the study, and 1 could not tolerate the light exposure. There were no adverse events. The participants were well matched with regard to age and sex (Table 1). Bipolar participants had significantly worse sleep quality (PSQI score—BDI: 5.8 ± 2.7; HC: 4.2 ± 2.2; $p = .002$) and a significantly lower MEQ score (BDI: 51.1 ± 7.8; HC: 57.1 ± 8.8; $p = .003$), indicating a tendency toward evening preference (both values are within the "neither range"). During the week preceding the study, participants with bipolar disorder woke up approximately 28 minutes later than HC subjects (BDI: 7:14 AM ± 1:03 hours; HC: 6:46 AM ± 0:53 hours; $p = .023$).

Phase Shift and DLMO

Melatonin concentrations were too low to reliably determine DLMO in 4 of the 87 participants ($n = 1$ HC; $n = 3$ BDI). Narrow bandwidth blue light exposure for 2 hours starting at 9:00 PM led to a mean phase shift (comparing DLMO from T1 to T3) in DLMO of 25.9 ± 38.6 minutes ($n = 83$). There was a significantly larger phase shift in participants with bipolar disorder (31.2 ± 43.3 min, $n = 29$) compared with HC subjects (22.6 ± 36.0 min, $n = 54$) ($F_{1,82} = 4.110$; $p = .046$) (Figure 1). Effect size was small to moderate ($\eta^2 = 0.49$).

Bipolar participants were circadian phase delayed compared with the HC subjects (DLMO: BDI = 8:44 PM ± 0.93 hours; HC = 8:12 PM ± 0.74 hours; $p = .091$) as measured at T1. Phase measured by DLMO on T1 was significantly inversely correlated with phase shift ($r = -0.46$, $n = 83$, $p < .001$) (Figure 2).

There were no significant correlations between the degree of phase shift and age ($r = 0.14$; $p = .25$), PSQI score ($r = 0.07$; $p = .56$), MEQ ($r = -0.188$; $p = .105$), or Global Assessment of Functioning ($r = -0.08$; $p = .47$). Sex had no influence on the phase shift magnitude ($F_1 = 0.046$; $p = .831$).

Lithium treatment did not significantly affect the magnitude of light-induced phase shift among patients with BDI ($F_1 = 1.270$; $p = .270$) (Table S3).

Within the BDI group, there were no significant correlations between the degree of phase shift and the clinical parameters, age of onset ($r = 0.218$; $p = .264$), number of depressive episodes ($r = 0.235$; $p = .229$) or manic episodes

Table 1. Demographic, Clinical, and Chronobehavioral Characteristics of HC Subjects and Patients With BDI

Characteristics	HC Subjects, $n = 55$	Patients With BDI, $n = 32$	p Value[a]
Age, Years	41.5 (9.5)	42.6 (11.0)	.609
Sex, Female	56%	53%	.773[b]
PSQI Score	4.2 (2.2)	5.8 (2.7)	.002
MEQ Score	57.1 (8.8)	51.1 (7.8)	.003
GAF Score	99.9	83.9	<.001
Bedtime, Last 7 Days	10:30 PM (2:57 hours)	9:46 PM (3:36 hours)	.708
Wake-up Time, Last 7 Days	6:46 AM (0:45 hours)	7:14 AM (1:05 hours)	.023
Daylight Exposure, on First Study Day	1.85 hours (1.85 hours)	2.12 hours (1.36 hours)	.516
Education, Qualified for Higher Education	65.5%	56.3%	.458[b]
Positive Family History[c]	0%	15.6%	N/A
Age of Onset, Years	N/A	20.9 (8.3)	N/A
Number of Depressive Episodes	N/A	9.7 (9.7)	N/A
Number of Manic Episodes	N/A	4.7 (4.6)	N/A
Current Medication			
Lithium	–	50%	N/A
Valproate	–	9.4%	N/A
Lamotrigine	–	18.8%	N/A
Atypical antipsychotics	–	46.9%	N/A
Antidepressants	–	18.8%	N/A
Oral contraceptive	3.1%	7.3%	.470[b]

Values are presented as mean (SD) or percentage.

BDI, bipolar I disorder; GAF, General Assessment of Functioning; HC, healthy control; MEQ, Morningness-Eveningness Questionnaire; N/A, not applicable; PSQI, Pittsburgh Sleep Quality Index.

[a]Two tailed *t* test, unless stated otherwise.

[b]χ^2 test.

[c]Parental history of bipolar disorder, unipolar depression, or schizophrenia.

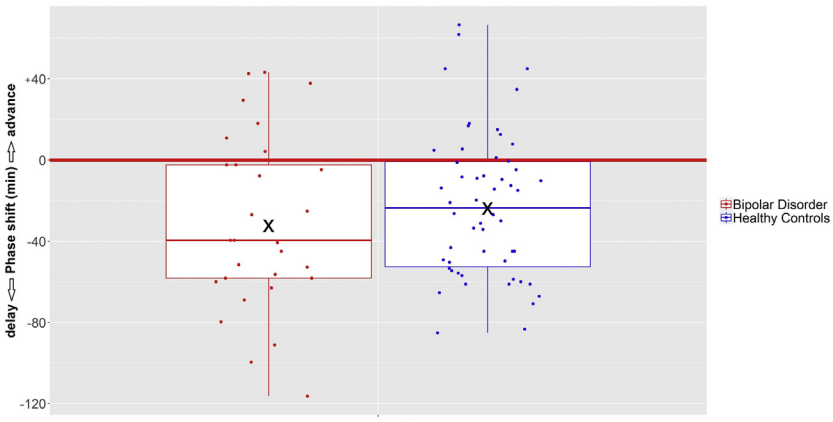

Figure 1. Boxplots comparing phase shift (min) in healthy control subjects (n = 53) and euthymic patients with bipolar I disorder (n = 29) following narrow bandwidth blue light (478 nm, half bandwidth = 18 nm, photon flux = 1.29 × 10^{15} photons/cm^2/s) administration for 120 minutes. For full details of the light source and light administration, see Methods and Materials, Figures S1–S4, and Tables S1 and S2.

(r = −0.265; p = .174), or number of suicide attempts (r = −0.76; p = .702).

The participants with BDI described a significantly higher degree of seasonality (SPAQ: 8.6 ± 4.2) than HC participants (5.4 ± 3.5) (t_{81} = 3.58; p = .001). Within the subgroup of participants with BDI, seasonality was nonsignificantly inversely related to phase shift (r = −0.121; p = .279) (Figure S6).

PER3 VNTR

The observed genotype frequencies of our sample were 35.5% ($PER3^{4/4}$), 51.6% ($PER3^{4/5}$), and 12.9% ($PER3^{5/5}$) for patients with BDI and 32.7% ($PER3^{4/4}$), 50.9% ($PER3^{4/5}$), and 16.4% ($PER3^{5/5}$) for HC subjects. The *PER3* VNTR polymorphism was thus equally distributed between participants with BDI and HC subjects (χ^2_2 = 0.204; p = .903).

There was no significant interaction of *PER3* VNTR genotype with the magnitude of phase shift (H_2 = 2.526; p = .283; n = 87) or baseline phase (DLMO at T1) (H_2 = 2.965; p = .227; n = 87).

Pupillometry

There were no differences in average pupil diameter during light exposure (t_{83} = 1.13; p = .26) (Figure S7) between the study groups.

DISCUSSION

To our knowledge, this study is the first to quantify the propensity of euthymic patients with a diagnosis of BDI to phase shift in response to evening light exposure under highly standardized conditions in comparison with HC participants. Bipolar participants exhibited a significantly larger light-induced phase

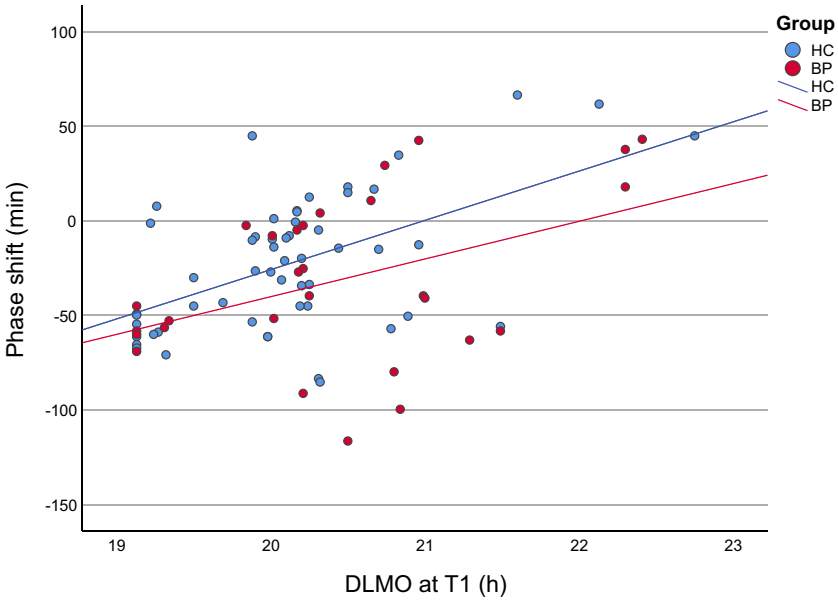

Figure 2. Scatterplot and separate trendlines comparing dim light melatonin onset (DLMO) at T1 and phase shift following light administration in healthy control (HC) subjects (n = 53) and patients with bipolar disorder (BP) (n = 29).

delay. This finding may help to explain the clinical observation that patients with bipolar disorder have an impaired ability to maintain stable circadian rhythms (6,54). This supersensitivity to phase shift may also underly other observations, such as the increased likelihood of relapse following transmeridian travel, particularly in a western direction (11); the earlier age of onset of bipolar disorder in regions with rapid spring time changes in solar insolation (10); and the profound intraindividual shifts in endogenous phase that occur during mood episodes (3,4).

A higher tendency to phase delay has also been described as a risk factor for seasonal affective disorder (55). Although an elevated seasonality as measured by the SPAQ was present in our sample, this did not significantly correlate with the light-induced phase shift.

The hypothesis tested in this strictly controlled euthymic sample aimed to establish a supersensitivity to phase delay as a potential trait marker of BDI. The differences between euthymic participants with bipolar disorder and HC subjects, although statistically significant, are moderate. Other studies assessing circadian mechanisms in affective disorders have also suggested a state-related component of individual circadian phase (4) and seasonal effects of light-induced melatonin suppression (56). In our study, however, no conclusions regarding possible state-related changes can be drawn. Pursuing this avenue may be valuable because animal research has suggested that a complex separation of endogenous oscillators (bifurcation) may be active in mania (57). It should also be noted that no conclusions regarding general phase stability or propensity to phase advance (i.e., by applied early morning light) can be drawn from this study.

Within the subsample of participants with bipolar disorder, no associations with clinical parameters were observed, and there was no evidence that increased propensity to phase delay was associated with the severity of the disorder. Increased phase delay may therefore be an unspecific feature of BDI, or larger samples of patients with bipolar disorder will be required to reveal such associations.

Modulation of the disease course and onset may also be related to nonvisual light processes other than those involved in circadian timing. Light in the melanopsin range (primarily blue light) activates several neural circuits vital for emotional processing within seconds or minutes compared with other light wavelengths (58–60). Patients with bipolar disorder may have altered responses in these nonvisual, noncircadian networks. Further studies using functional magnetic resonance imaging or electrophysiological measurements would be suitable to explore this hypothesis in this study population. The differential activation of alternative central nervous system networks may also explain why we found participants with BDI in this sample to be more prone to phase delay but participants with BDI in a separate sample not to display enhanced melatonin suppression (18).

A large interindividual variability in the light-induced phase shift was observed. This may in part be due to inherent interindividual differences in the responsiveness to phase shifting by light (61). In addition, approximately 8% of the participants (BDI and HC) displayed a substantial phase advance (>30 min), which in some cases may have been due to incomplete adherence to the study protocol. A study involving several successive days in highly standardized lighting conditions in the laboratory may have minimized this interindividual variation and improved compliance. Most participants with bipolar disorder, however, are employed and have families, considerably limiting their willingness or ability to remain in the laboratory for several successive days.

All participants with bipolar disorder were receiving mood-stabilizing medication. Both lithium and valproate have been shown to reduce melatonin suppression by nighttime light exposure (62,63). Lithium in particular is known to have wide-ranging effects on the circadian system (64). True differences between the study groups may therefore have been masked or exacerbated by the effects of the mood-stabilizing medication. Participants receiving lithium exhibited an increased phase delay, although not statistically significant; the study was not powered to reliably detect such a difference. Analogous to other chronobiological studies in bipolar disorder, it is neither feasible nor ethical to discontinue mood-stabilizing medication. Indeed, if an altered phase response to light were a true endophenotype, healthy unaffected first-degree relatives may be a suitable study group to test this hypothesis without the confounding effect of medication.

The current novel method of light exposure (light intensity adjusted in relation to pupil diameter) has not been applied in practice before and is based on theoretical calculations regarding the number of photons passing through the ocular lens. Incorrect assumptions regarding the underlying physics and physiology could significantly affect the results. However, because no significant differences in pupil diameter between the study groups were observed, the mean total light exposure was identical between the study groups (Figures S1–S4 and S7; Tables S1 and S2). In contrast to other protocols using light exposure, the continuous pupil monitoring also ensured patients could not close their eyes or sleep.

The study has some limitations that ought to be taken into account. As with every cross-sectional study, no inferences regarding causality or temporal relationships can be drawn. Longitudinal studies in high-risk cohorts will have to be undertaken to determine whether an increased propensity to phase delay can be considered a risk factor for bipolar disorder.

Although it is known that some individuals produce very low levels of melatonin, further melatonin sampling from midnight to 1 AM may have allowed for DLMO calculation in the 4 participants whose data could not be analyzed. The study design that did not control for light exposure in the interval between T2 and T3 may have worked against a phase delay because a proportion of participants will have been exposed to light early the following morning. An improved study design would ideally include constant and dim light conditions following T2.

Our current knowledge of circadian physiology and light in the melanopsin range as major zeitgeber would suggest that the light exposure was the most relevant factor in causing phase delay. However, a control condition (i.e., using dim red light) could have helped to establish with greater certainty that no other parts of the study protocol were the determining factors with regard to phase shift.

Persons with extreme chronotype (delayed sleep-wake phase disorder) are known to be more sensitive to the phase-delaying effects of evening and nighttime light exposure (65). A portion of the observed difference may therefore be attributable to the later mean chronotype found in our BDI sample.

Although the sample size is acceptable considering the experimental setup and in comparison with similar chronobiology studies in patients with bipolar disorder, there was a higher-than-anticipated interindividual variation. This substantial interindividual variability could presumably be reduced by a multiday study setup in controlled conditions safeguarding protocol adherence and minimizing potentially distorting circadian stimuli. However, as previously mentioned, this is not always feasible in this study population. Replication studies should attempt to recruit larger samples. In addition, the study was not powered to detect associations of phase delay with clinical characteristics and thus some associations may have been missed.

In conclusion, using a novel method of light administration, our study showed that euthymic patients with BDI have a significant supersensitivity to light-induced phase delay compared with a matched HC group.

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DJS is a coinventor on two issued patents (EP 1614441A1 and EP3055022A). All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry and Psychotherapy (PR, BS, CS, AY, LB, MR, KK, MB, SN), University Hospital Carl Gustav Carus, Technische Universität Dresden; Chair of Power Electronics (HG, FW), Institute of Electrical Power Engineering, TU Dresden, Dresden, Germany; and Chronobiology (DJS), Faculty of Health and Medical Sciences, University of Surrey, Guilford, United Kingdom.

Address correspondence to Philipp Ritter, M.B.B.S., at Philipp.Ritter@uniklinikum-dresden.de.

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