Psychological Medicine (2017), **47**, 1678–1689. © Cambridge University Press 2017
doi:10.1017/S0033291717000186

ORIGINAL ARTICLE

Sleep and circadian rhythm disturbance in bipolar disorder

A. J. Bradley[1,2], R. Webb-Mitchell[1], A. Hazu[1], N. Slater[1], B. Middleton[3], P. Gallagher[1], H. McAllister-Williams[1,4] and K. N. Anderson[5]*

[1] *Institute of Neuroscience, Newcastle University, Wolfson Research Centre, Campus for Aging and Vitality, Newcastle Upon Tyne, UK*
[2] *Eli Lilly and Company Limited, Lilly House, Basingstoke, UK*
[3] *Surrey Sleep Research Centre and Centre for Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK*
[4] *Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle, UK*
[5] *Regional Sleep Service, Freeman Hospital, High Heaton, Newcastle upon Tyne, UK*

Background. Subjective reports of insomnia and hypersomnia are common in bipolar disorder (BD). It is unclear to what extent these relate to underlying circadian rhythm disturbance (CRD). In this study we aimed to objectively assess sleep and circadian rhythm in a cohort of patients with BD compared to matched controls.

Method. Forty-six patients with BD and 42 controls had comprehensive sleep/circadian rhythm assessment with respiratory sleep studies, prolonged accelerometry over 3 weeks, sleep questionnaires and diaries, melatonin levels, alongside mood, psychosocial functioning and quality of life (QoL) questionnaires.

Results. Twenty-three (50%) patients with BD had abnormal sleep, of whom 12 (52%) had CRD and 29% had obstructive sleep apnoea. Patients with abnormal sleep had lower 24-h melatonin secretion compared to controls and patients with normal sleep. Abnormal sleep/CRD in BD was associated with impaired functioning and worse QoL.

Conclusions. BD is associated with high rates of abnormal sleep and CRD. The association between these disorders, mood and functioning, and the direction of causality, warrants further investigation.

Received 14 July 2016; Revised 12 January 2017; Accepted 12 January 2017; First published online 8 February 2017

Key words: Bipolar, circadian rhythm, cognition, melatonin, sleep.

Introduction

Subjective reports of various types of sleep disturbance are described in all phases of bipolar disorder (BD), including remission (Harvey *et al.* 2005; Harvey, 2008; Kaplan *et al.* 2011; Kanady *et al.* 2015; Ng *et al.* 2015) but with substantial variability in prevalence between studies. Meta-analyses of studies objectively estimating sleep variables in remitted BD patients demonstrated prolonged total sleep time (TST), increased wakenings after sleep onset greater variability of sleep–wake variables and reduced sleep efficiency (Geoffroy *et al.* 2014; Ng *et al.* 2015). These meta-analyses highlighted that there has also been little consistency in the way sleep and circadian rhythm has been measured and assessed. Studies have used a range of actiwatches and algorithms for calculating sleep and wake estimates and utilized variable recording periods, making comparisons across studies challenging. There is a need for methodological improvements, including longer recordings to allow improved analysis of circadian rhythm measures. Thus it is currently unknown what proportion of sleep disorder relates to a circadian rhythm disorder (CRD). Furthermore, none of the published actigraphy studies in BD have performed respiratory sleep studies to screen for primary sleep disorders, such as obstructive sleep apnoea (OSA), that may additionally contribute to hypersomnia and sleep fragmentation. The aim of this study was to describe the different sleep–wake phenotypes in an opportunistic cohort of patients with BD and age-matched healthy controls with a comprehensive battery of objective and subjective assessments of sleep and circadian variables, including urinary melatonin levels and respiratory sleep studies analysis.

Method

Participants

The study was approved by the National Research Ethics Service Committee North East – Newcastle & North Tyneside. Outpatients with BD type I or II, in any mood state, were recruited from a research

* Address for correspondence: Dr K. N. Anderson, Regional Sleep Service, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN, UK.
(Email: kirstie.anderson@nuth.nhs.uk)

database, patient support groups, and NHS services in the North East of England. Healthy controls, matched by age and gender, were recruited from Newcastle University, local volunteer databases and hospital staff and their families. All participants provided written informed consent before taking part in the research. Participants were aged 18–65 years, fluent in English and able to provide consent. Exclusion criteria were: verbal IQ <90 assessed with the National Adult Reading Test (NART; Nelson, 1982), any significant medical or neurological disorder that might interfere with sleep or cognition, current alcohol or substance misuse disorder (defined with DSM-IV criteria; APA, 2000), current shift work and previous significant head injury. A BD diagnosis meeting DSM-IV criteria was confirmed using the Mini International Neuropsychological Interview (MINI; Sheehan *et al.* 1998). Patients with BD were excluded if they had had any changes to their psychotropic medication in the previous 4 weeks. Exclusion criteria for controls were: personal or first-degree relative's history of a DSM-IV Axis I disorder as determined by clinical history, prescribed psychotropic medications and any known sleep disorder. Additionally controls had to be psychiatrically well, confirmed by MINI interview, have a Hamilton Depression Rating Scale (HAMD-17) score <7, a Young Mania Rating Scale (YMRS) score <5, a Pittsburgh Sleep Quality Index (PSQI) score <5 and an Epworth Sleepiness Scale (ESS) score <10.

Overall study design

The study was cross-sectional, with participants assessed over a 3-week period.

Psychiatric symptoms and subjective sleep assessments

Participants were assessed on days 1 and 21. A comprehensive battery of questionnaires and rating scales were used to assess mood, anxiety and functioning. These included: the 17-item GRID-HAMD (Williams *et al.* 2008), Beck Depression Inventory (BDI; Beck *et al.* 1961), YMRS (Young *et al.* 1978), the State and Trait Anxiety Inventory (STAI; Spielberger *et al.* 1983), the Functioning Assessment Short Test (FAST; Rosa *et al.* 2007). Quality of life (QoL) was assessed with the BD-specific scale, the QoL.BD (Michalak & Murray, 2010). Subjective sleep and circadian rhythm was assessed using: the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN; Giglio *et al.* 2009), the PSQI where a score >5 indicates clinically significant poor sleep quality (Buysse *et al.* 1989) and the ESS where a score $\geqslant$10 indicates excessive daytime sleepiness (Johns, 1991). A short version of the morningness/eveningness questionnaire (Horne & Ostberg, 1976) was also used on day 1 of the study to assess chronotype. All medications used by the patients in the BD group were recorded.

Assessment for sleep apnoea

A single night of home partial polysomnography, using the Embletta Gold Polygraphy System (Embla Systems, USA), was used to screen for sleep apnoea. Respiratory events were scored according to the standard criteria of the American Association of Sleep Medicine (AASM; Kushida *et al.* 2005) and the apnoea hypopnoea index (AHI) and oxygen desaturation index (ODI) derived. An AHI of >5/h was considered abnormal and indicative of sleep apnoea. Severity was defined as mild (AHI 5–15), moderate (AHI 15–30) or severe (AHI >30).

Assessment for Restless Legs Syndrome (RLS)

Participants completed the Restless Legs Syndrome Rating Scale to assess for the presence and severity of RLS (Walters *et al.* 2003). This scale includes 10 questions each scoring 0–4 with a score of 1–10 representing mild RLS, 11–20 moderate RLS, 21–30 severe RLS and 31–40 very severe RLS.

Assessment of sleep–wake cycle

Subjects wore a triaxial wrist accelerometer (GENEActiv; Activinsights, UK) on their non-dominant wrist for all 21 days of the study and completed a daily sleep log recording lights out, out of bed time and any daytime naps. Unlike older actigraphs which record movement in brand-specific activity counts modern accelerometers record high-resolution data in universal units of gravitational acceleration (raw accelerometry). These data can be analysed to estimate both physical activity and sleep. Data recorded in SI units rather than brand-specific activity counts allows for the comparison of data recorded from any brand of device which records in SI units and therefore allows direct comparisons between studies and the pooling of data (te Lindert & Van Someren, 2013). In this study the accelerometer was set to sample at 30 Hz in order that the battery would continuously record for a period of at least 21 days. The raw accelerometer data was analysed using an open source R package sleep detection algorithm, GGIR, that has already demonstrated a high sensitivity and specificity to detect periods of sleep (van Hees *et al.* 2015). This algorithm uses a novel method of accelerometer-derived arm angle to detect sleep. Estimated arm angles are averaged per 5-s epoch and used to assess change in arm angle between successive 5-s epochs. Periods of time during which

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

there is no change in arm angle >5° over at least 5 min are classified as bouts of sustained inactivity, or potential sleep periods. The algorithm utilizes the sleep log to distinguish nocturnal sleep from daytime naps. The following variables were derived: sleep onset time, sleep offset time, TST, time in bed (TIB), sleep efficiency (defined as TST/TIB) and mean 24-h sleep duration (defined as nocturnal sleep plus daytime naps). Intra-subject variability in sleep variables was defined by the between night standard deviation over the assessment period for individual participants. Correlation analysis was performed to check agreement between sleep logs and accelerometer-derived sleep variables. The relative amplitude between day and night activity was calculated from mean acceleration recorded in milli gravitational units (milli-g) during the least active 5 h (L5) and most active 10 h (M10) according to previously published methods (Van Someren *et al.* 1999). Using both accelerometry-derived sleep estimates and the visual sleep–wake actograms produced by the algorithm participants were then identified as normal sleepers (6–10 h sleep within 24 h with a regular sleep–wake cycle), short sleepers (<6 h nocturnal sleep), long sleep (>10 h sleep within 24 h) and circadian rhythm disturbance evidenced by either a delayed sleep phase (habitual sleep onset after 2 a.m.), advanced sleep phase, an irregular sleep–wake pattern (3–4 periods of sleep but no consolidated overnight period) or a non-24-h pattern in keeping with the circadian rhythm types within the International Classification of Sleep Disorder – 3rd edn (ICSD-3; American Academy of Sleep Medicine, 2014). Therefore those sleeping >3 h outside of societal norms, e.g. habitual sleep time 3 a.m., or rise time that varied day to day by >3 h in the absence of shift work. Those sleeping <6 h or >10 h were also defined as abnormally short or long sleepers again based on the normative sleep period defined within ICSD-3.

Melatonin measurement

To further explore possible mechanisms of circadian dysfunction 6-sulphatoxymelatonin (aMT6s) was measured. This metabolite of melatonin, was measured in urine over a 48-h period, once during the first week of the study period and once during the third week of the study period with analysis according to previously published protocols (Wulff *et al.* 2006).

In brief, participants recorded the time of their last toilet visit and then passed each subsequent full volume of urine into a measuring jug at 4-h intervals (or 8 h overnight) for the next 48 h. The total volume of urine and exact clock time it was passed were recorded and a 5-ml sample taken and stored at −20 °C before being sent for analysis by radioimmunoassay to determine aMT6s concentrations (Aldhous & Arendt, 1988).

Statistical analysis

All statistical analyses were performed using SPSS statistical package v. 22 (IBM Corp., USA). Normality of distribution of data was tested using the Shapiro–Wilk test. Log_{10} or square-root transformations were used where necessary to normalize the data. Parametric tests were used unless the data remained non-normally distributed despite transformation when equivalent non-parametric tests were used. A significance threshold of $p < 0.05$ was used for all analyses. The aMT6s profiles were evaluated using cosinor analysis, based on the least square approximation of the time series using a cosine function with a period of 24 h (Minors & Waterhouse, 1988) and the following parameters obtained: acrophase time – time of the peak aMT6s concentration or maximum of the fitted cosinor function; mesor – mean aMT6s value for all the samples included in the cosinor analysis; and amplitude – difference between the mesor and the peak aMT6s concentrations. Two estimates of 'goodness of fit' were used to determine the validity of the cosinor-derived indices: (i) the percentage rhythm or percentage data variability accounted for by the cosine curve: 100% rhythm = all data points fall on the cosine curve; 0% rhythm = none of the data points falls on the cosine curve and (ii) the likelihood of the data points fitting a straight line as opposed to a cosine curve, expressed as a p value. Data were considered acceptable if the % rhythm was $\geqslant 50$ and the cosinor fit was significant at the 95% level ($p < 0.05$) (Minors & Waterhouse, 1988).

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Participants

Eighty-eight participants, 46 with BD (16 BD I, 30 BD II) and 42 controls, completed the study protocol and provided accelerometer data [mean 19.7 (S.D.=3.0) days]. Table 1 shows the participants' characteristics. Groups did not differ significantly with regard to age or gender but participants with BD had a greater body mass index (BMI), were more likely to be unemployed, and scored more highly on mood and

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

Table 1. *Characteristics of participants*

			Test statistics		
	Controls ($n = 42$)	BD ($n = 46$)	χ^2 (df)	Mann–Whitney U	p
Female gender, n (%)	29 (69)	31 (67.4)	0.028 (1)		0.868
Age, years, mean (S.D.)	42.5 (11.9)	46.8 (11.1)		768.0	0.098
(range)	(19–64)	(23–64)			
BMI, kg/m^2, mean (S.D.)	25.6 (4.8)	30.0 (6.7)		538.0	0.001
(range)	(19.5–39.7)	(21.0–52.0)			
Currently employed, n (%)	34 (81)	23 (50)	9.218 (1)		0.002
Chronotype, n (%)					
Morning	19 (45.2)	14 (30.4)	4.449 (2)		0.108
Evening	3 (7.1)	10 (21.7)			
Neither type	20 (47.6)	22 (47.8)			
HAMD-17, mean (S.D.)	0.3 (0.6)	9.1 (7.2)		49.0	<0.001
(range)	(0–2)	(0–35)			
HAMD without sleep items, mean (S.D.)	0.24 (0.53)	7.0 (6.2)		59.0	<0.001
(range)	(0–2)	(0–30)			
BDI (S.D.)	0.6 (1.6)	12.2 (11.5)		127.5	<0.001
(range)	(0–9)	(0–49)			
BDI without sleep item, mean (S.D.)	0.6 (1.6)	11.3 (11.1)		169.0	<0.001
(range)	(0–9)	(0–47)			
YMRS, mean (S.D.)	0.1 (0.4)	0.9 (2.2)		839.0	0.075
(range)	(0–2)	(0–10)			
STAI-S (S.D.)	23.6 (4.0)	35.1 (12.8)		345.5	<0.001
(range)	(20–34)	(20–73)			
STAI-T	24.6 (7.1)	44.0 (14.7)		206.0	<0.001
(range)	(20–54)	(21–77)			
PSQI Global score, mean (S.D.)	2.2 (1.3)	8.6 (4.6)		138.5	<0.001
(range)	(0–4)	(1–18)			
ESS, mean (S.D.)	3.8 (2.5)	6.2 (4.9)		680.5	0.016
(range)	(0–9)	(0–21)			
BRIAN, mean (S.D.)	20.4 (3.2)	40.1 (13.6)		122.500	<0.001
(range)	(18–30)	(18–65)			
FAST, mean (S.D.)	3.9 (6.2)	23.2 (17.4)		211.500	<0.001
(range)	(0–22)	(0–72)			
QoL.BD, mean (S.D.)	215.3 (20.2)	157.7 (39.5)		167.500	<0.001
(range)	(162–263)	(50–235)			

BD, Bipolar disorder; S.D., standard deviation; df, degrees of freedom; BMI, body mass index; HAMD-17, 17-item Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; YMRS, Young Mania Rating Scale; STAI-S/T, State and Trait Anxiety Inventory – State/Trait; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BRIAN, Biological Rhythms Interview of Assessment in Neuropsychiatry; FAST, Functional Assessment Short Test; QoL.BD, Quality of Life in Bipolar Disorder Questionnaire, morning and evening chronotypes include both definite and moderate subtypes.

anxiety ratings and lower on QoL. Twenty-one participants with BD scored $\geqslant 8$ on the HAMD-17 (range 8–35), but none of the patients were considered clinically to be manic or hypomanic for the duration of the study (YMRS range 0–10).

Subjective description of sleep

On the PSQI, patients with BD scored on average 6.4 points higher than healthy controls (Table 1), with 30 (65.2%) scoring $\geqslant 5$, indicative of some form of sleep disturbance (note that a PSQI score of $\geqslant 5$ was an exclusion criteria for healthy controls). Many patients with BD described subjective problems with their sleep. Their average score across the three HAMD-17 sleep items was 2.13 (S.D.=1.9), with 12 (26.1%) patients scoring $\geqslant 4$. The ESS, validated for identifying excessive daytime sleepiness, was >10 in nine BD patients. In terms of chronotype, the BD group contained more participants with an evening preference than the control group but the difference was not statistically significant (χ^2=4.449, $p = 0.108$).

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

Sleep apnoea

Forty-one of 46 participants with BD and 40 of the 42 controls completed the overnight partial polysomnography providing good quality respiratory data. Significantly more participants with BD than controls had OSA [BD: $n = 12$ (29%), controls $n = 4$ (10%); χ^2=4.742, $p = 0.029$]. Four participants with BD had moderately severe OSA (AHI 15–30) but no participant in either group had severe sleep apnoea (AHI >30). One participant with BD was already on continuous positive airways pressure (CPAP) treatment for known OSA and was therefore counted as AHI <5 and hence with 'normal' sleep. The BD patients with OSA were older than normal BD sleepers (44 years *v.* 51 years, $p = 0.054$).

Two participants with BD with moderately severe OSA went on to successfully start treatment with CPAP with a decrease in ESS on therapy recorded.

RLS

Two participants with BD, but no controls, reported moderate or severe restless legs symptoms.

Accelerometry-defined sleep–wake cycles

Compliance with the accelerometry was very good with the mean number of nights of data collected being 20.1 for controls and 19.2 for the BD group. Accelerometry measures showed participants with BD spent significantly longer TIB, have significantly longer nocturnal sleep time and also more unstable and variable sleep–wake patterns, alongside longer daytime napping periods, than those in the control group (see Table 2). Compared to controls participants with BD spent around 51 min per night longer in bed, spent 24 min longer asleep at night and had lower sleep efficiency. Daytime napping/sedentary behaviour was also on average significantly longer by 29 min/day in participants with BD. The relative amplitude between the most active 10 h and least active 5 h was significantly lower in the participants with BD than controls, driven primarily by significantly lower M10 activity. The intra-subject variability in all sleep variables was significantly greater in participants with BD, indicating instability in sleep–wake patterns compared to controls.

Visual representations of typical actograms are shown in Fig. 1. The actograms could clearly distinguish different sleep–wake patterns. Using the definitions described above, 23 of the BD patients had normal sleep length and 23 had abnormal sleep length or CRD. Four (2.2%) were short nocturnal sleepers (<6 h) and 14 (30.4%) were long sleepers (>10 h) over each 24-h period. Within the long sleepers, this included daytime naps. Twelve (26.1%) had CRD including delayed sleep phase pattern ($n = 3$), advanced sleep phase pattern ($n = 1$), irregular sleep–wake phase ($n = 3$) non-24 h sleep/wake phase disorder ($n = 4$) and circadian sleep–wake disorder not otherwise specified ($n = 1$). This compared with just four control participants with CRD, one with an advanced sleep phase and three with delayed sleep phase. There was significant overlap between the various sleep patterns and circadian dysrhythmia as shown in Fig. 2. Two of the four BD patients who were short sleepers and six of the 14 long sleepers also had evidence of CRD. OSA was also a potential explanation of long sleep in five patients with BD.

Melatonin assays

Thirty-nine controls and 38 BD participants provided at least one urine collection that had a clear melatonin rhythm assessed with cosinor analysis. An additional two participants with BD provided good samples but had a 24-h aMT6s output that was too low to detect a rhythm (<3 μg/24 h). Fifty-seven (30 controls, 27 BD) participants provided two urine samples allowing a period to be calculated. Two participants in the control group and five BD participants had a non-24-h melatonin period (defined as $\geqslant$24.2 h or $\leqslant$23.8 h). Controls demonstrated a significantly greater aMT6s secretion (μg/24 h) than the BD group [18.0 (S.D. = 9.1) *v.* 12.8 (S.D. = 8.5); Mann–Whitney=476.0, $p = 0.003$], a greater mesor (μg) (rhythm-adjusted mean) [controls 12.1 (S.D.=6.1) *v.* BD 9.0 (S.D.=6.0); $t = 2.56$ (75), $p = 0.012$] and amplitude (μg) [controls 14.5 (S.D.=8.0) *v.* BD 9.8 (S.D. 7.7); $t = 3.03$ (75), $p = 0.003$]. Control participants also differed from BD participants in that they demonstrated a significantly earlier mean acrophase (h) (time of peak aMT6s concentration) which was on average 1 h 26 min earlier [controls 3.24 (S.D. = 1.88) *v.* BD 4.67 (S.D. = 2.23); Mann–Whitney U=476.0, $p = 0.004$]. The later acrophase in the BD group is indicative of a delayed biological rhythm compared to the controls, in keeping with the larger number of evening chronotypes in the BD group (see Table 1).

Comparison of mood, sleep, function, QoL and melatonin in normal and abnormal sleeping BD patients

Differences in mood, anxiety, psychosocial function and QoL were explored within the BD group comparing those with accelerometer-defined normal ($n = 23$) and abnormal sleep ($n = 23$) (Table 3). There were no statistically significant differences in age, BMI, numbers with OSA or mean AHI, mood or anxiety between the groups. Abnormal sleepers subjectively rated their sleep as lower quality than normal sleepers on the

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

Table 2. *Summary accelerometer data*

			Test statistic		
	Controls ($n = 42$)	BD ($n = 46$)	*t* test (df)	Mann–Whitney *U*	*p*
TIB, h (S.D.)	7.85 (0.77)	8.69 (1.48)		562.000	0.001
Intra-subject variability in TIB	1.19	1.72	−3.016 (86)		0.003
Nocturnal sleep time (S.D.)	6.92 (0.70)	7.33 (1.20)		664.000	0.012
Intra-subject variability in nocturnal sleep time	1.01	1.40	−3.386 (86)		0.001
Sleep efficiency (S.D.)	0.88 (0.04)	0.85 (0.75)		707.000	0.030
Intra-subject variability in sleep efficiency	0.049	0.069	−2.960 (86)		0.004
Daytime naps/sedentary behaviour (S.D.)	1.47 (0.86)	1.95 (1.05)	−2.246 (86)		0.027
Intra-subject variability in daytime naps/ sedentary behaviour	0.86	1.10	−2.336 (86)		0.022
Intra-subject variability in sleep onset time (h)	0.99	1.42		730.000	0.056
Intra-subject variability in sleep offset time (h)	1.29	2.24		694.000	0.023
L5 (S.D.)	6.0 (2.8)	5.9 (1.9)		923.000	0.719
M10 (S.D.)	47.8 (14.8)	37.8 (11.6)	3.508 (86)		0.001
Relative amplitude between day and night activity (S.D.) (M10–L5)	0.77 (0.10)	0.71 (0.13)		698.000	0.025
Mean acceleration (milli-g) (S.D.) per 24 h	30.77 (9.1)	23.77 (6.6)	4.119		<0.001

BD, Bipolar disorder; TIB, time in bed; Intra-subject variability in sleep variables was defined by the between night standard deviation over the assessment period for each subject, daytime naps/sedentary behaviour is the sum of all time epochs that meet the algorithm defined sleep criteria but are outside of the nocturnal time window defined by the sleep diary; L5, mean acceleration over the least active 5-h window in each 24-h period; M10, mean acceleration in the most active 10-h window in each 24-h period.

PSQI although it is noteworthy that normal sleeping BD participants still scored in the clinically significant range for poor sleep quality (>5). BRIAN scores were also significantly greater in abnormal compared to normal sleepers indicating greater difficulty maintaining good 24-h rhythms. However, there was no significant difference in daytime sleepiness scores measured on the ESS with both groups scoring in the normal range (ESS <10).

While mood ratings did not differ between normal and abnormal sleeping groups, there was a significant correlation between both HAMD-17 and BDI scores (with sleep items removed) and PSQI total score in the BD group [Spearman's rank-order correlation: $r^2(46) = 0.413$, $p < 0.004$; $r^2(46) = 0.529$, $p < 0.001$, respectively], although no correlation between objective actigraphy measures and mood. There was, however, significantly poorer psychosocial functioning (*t* test 3.033, $p < 0.004$) and lower QoL (*t* test −2.495, $p = 0.016$) in abnormal *v.* normal sleeping patients with BD. These differences remained when covarying for either HAMD-17 (FAST: $F = 6.502$, df = 1,43, $p = 0.014$; QoL.BD: $F = 6.436$, df = 1,43, $p = 0.015$) or BDI (FAST: $F = 7.527$, $p = 0.009$; QoL.BD: $F = 8.839$, $p = 0.005$). Therefore abnormal sleep identified with actigraphy was associated with reduced function and QoL independently from mood.

The aMT6s 24-h secretion also differed significantly within the BD group. BD participants with normal sleeping patterns demonstrated significantly greater 24-h aMT6s secretion than abnormal sleeping participants (Table 2), but did not differ from normal sleeping controls [BD 15.8 (S.D.=9.1) *v.* controls 17.5 (8.3); Mann–Whitney U=266.0, $p = 0.367$].

The possible role of medication in sleep phenotype was explored. Significantly more long sleepers (42.9%) took hypnotics than normal sleepers (6.3%) (Fisher's exact test $p = 0.031$). There were no other significant differences in the medications between subgroups of patients (Supplementary Fig. S1). We did assess whether age of patient correlated with sleep–wake pattern. Abnormal sleepers were older than normal BD sleepers (49 years *v.* 43 years, $p = 0.029$). The BD patients with OSA were older than normal BD sleepers (51 years *v.* 44 years, $p = 0.054$). Otherwise there were no significant differences in age between normal sleepers and long sleepers or normal sleepers and CRD sleepers.

Discussion

This is the most comprehensive study to date to assess sleep and circadian rhythm in patients with BD compared to controls. Of the patients with objective

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

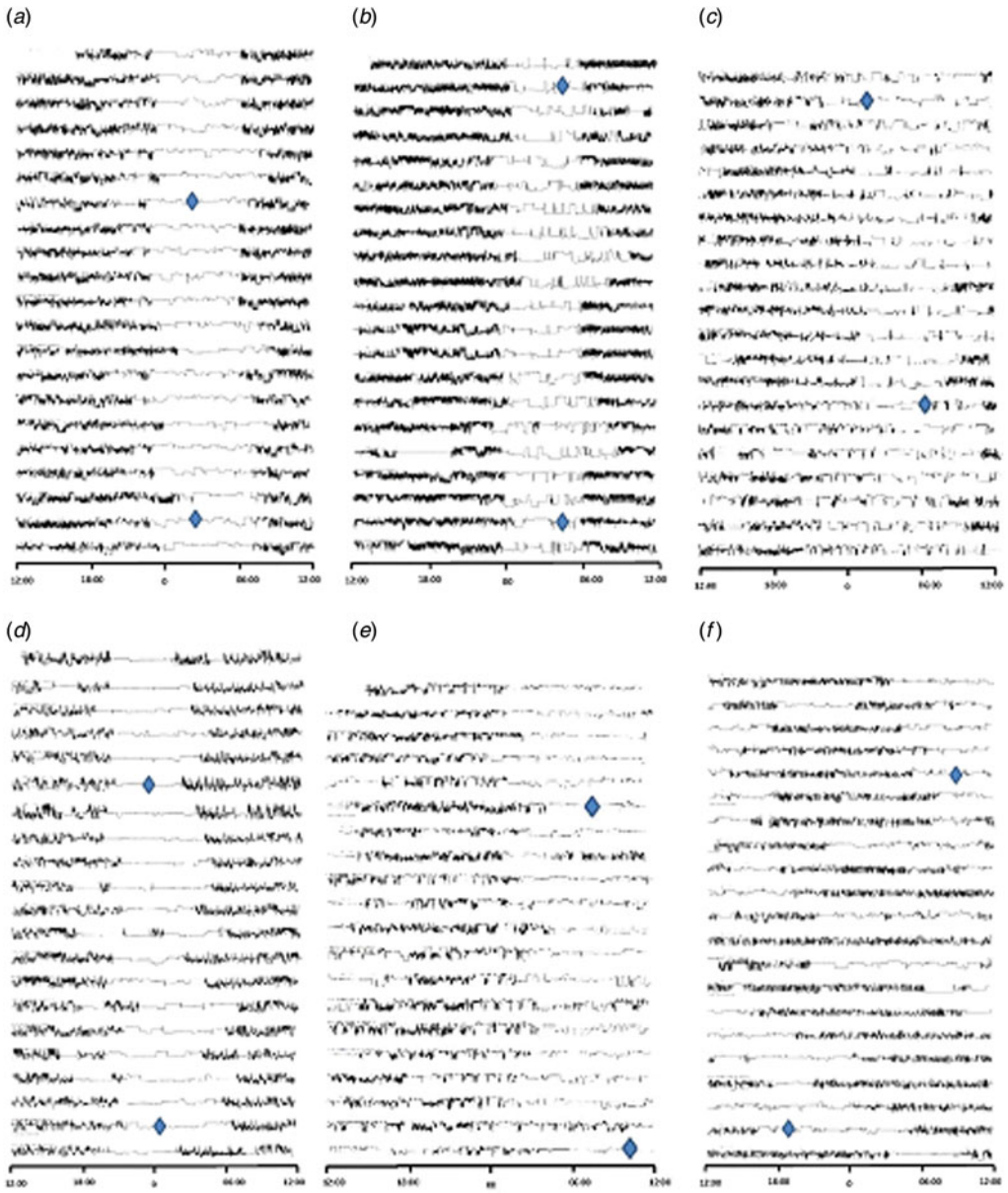

Fig. 1. Actograms demonstrating the sleep–wake cycle over 21 days and timing of 6-sulphatoxymelatonin (aMT6s) acrophase from six different sleep phenotypes. Actigraphic data are 48-h double-plotted with successive days on vertical axis starting at midday. The diamonds represent the timing of the acrophase of aMT6s taken at two different time points over the 21 days of actigraphy. This is a marker for the phase of the circadian clock. (*a*) Normal sleeper with a well entrained circadian rhythm. Mean nocturnal sleep duration = 6.9 h. (*b*) Short sleeper with a well entrained circadian rhythm. Mean sleep duration = 5.76 h. (*c*) Long sleeper mean sleep duration = 10.95 h. Note mildly irregular sleep–wake times and aMT6s period length = 24.40 h. (*d*) Advanced sleep phase with well entrained circadian rhythm. Mean sleep onset time = 20.25, mean nocturnal sleep duration = 7.23 h. (*e*) Delayed sleep phase with well entrained circadian rhythm. Mean sleep onset time = 01.43, mean nocturnal sleep duration = 08.59 h. (*f*) Non-24-h sleep–wake rhythm. Actogram demonstrated an irregular sleep–wake cycle with evidence of free-running sleep onset during the final 8 days. aMT6s period length = 24.40 h.

measures of abnormal sleep, a high proportion had CRD (26.1%) and there was considerable overlap between different sleep and circadian rhythm phenotypes. Abnormality in circadian rhythm in BD was further demonstrated in the BD group by significant differences in melatonin secretion compared to healthy controls, particularly a decreased 24-h output seen in the patients with abnormal sleep patterns. Those BD patients with abnormal sleep had similar mood symptoms to those with normal sleep but less stable biological rhythms, worse psychosocial functioning and reduced QoL.

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

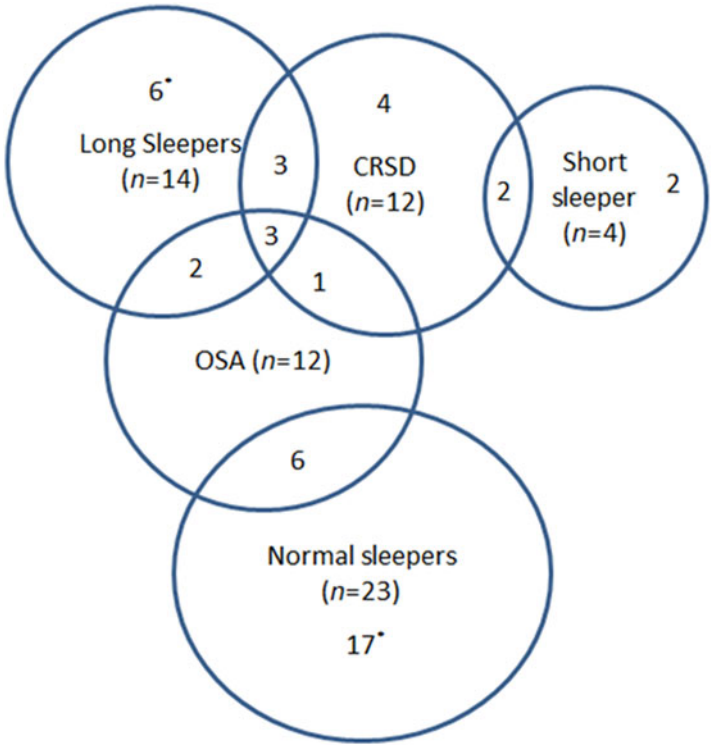

Fig. 2. Sleep phenotypes and their overlap in the bipolar disorder group. Normal sleepers = >6 and <10 h nocturnal sleep and no CRSD; long sleepers = total 24 h sleep >10 h; short sleepers = nocturnal sleep <6 h. CRSD, Circadian rhythm sleep disorder; OSA, obstructive sleep apnoea. * Three of the participants in the long-sleep-only cohort and two of the normal sleepers did not complete the test for sleep apnoea.

Table 3. *BD normal v. abnormal sleepers*

	BD normal sleeper ($n = 23$) Mean (S.D.)	BD abnormal sleeper ($n = 23$) Mean (S.D.)	Normal *v.* abnormal test statistics		
			t (df)	Mann–Whitney *U*	*p*
Age (years)	45.6 (11.0)	47.9 (11.2)		229.5	0.441
BMI (kg/m^2)	28.4 (4.5)	31.5 (8.1)	1.199 (44)		0.170
AHI	6.3 (8.7)	4.3 (5.0)		198.0	0.754
HAMD-17	7.8 (7.0)	10.4 (7.3)	1.659 (44)		0.104
BDI	10.0 (11.3)	14.4 (11.6)	1.770 (44)		0.084
YMRS	1.4 (2.8)	0.4 (1.3)		225.5	0.216
STAI-S	33.2 (14.4)	37.0 (10.9)	1.386 (44)		0.173
STAI-T	40.5 (13.8)	47.3 (14.8)	1.611 (44)		0.114
PSQI	6.9 (3.4)	10.4 (5.0)	2.733 (44)		0.009
ESS	5.6 (3.7)	6.9 (5.8)	0.643 (44)		0.524
BRIAN	35.7 (13.6)	44.5 (12.3)	2.285 (44)		0.027
FAST	16.7 (15.7)	29.7 (16.8)	3.033 (44)		0.004
QoL.BD	171.4 (37.9)	143.9 (36.9)	−2.495 (44)		0.016
Melatonin (normal sleeper $n = 19$, abnormal sleepers $n = 21$)					
aMT6s (μg/24 h)	15.8 (9.1)	10.0 (7.0)		108.0	0.013

BD, Bipolar disorder; BMI, body mass index; AHI, Apnoea Hypopnoea Index; PSQI, HAMD-17, 17-item Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; YMRS, Young Mania Rating Scale; STAI-S/T, State and Trait Anxiety Inventory – State/Trait; Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BRIAN, Biological Rhythms Interview of Assessment in Neuropsychiatry; FAST, Functional Assessment Short Test; Qol.BD, Quality of Life in Bipolar Disorder Questionnaire; aMT6s, 6-sulphatoxymelatonin.

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

The patients with BD in our study spent longer in bed, had more fragmented sleep and had more unstable and irregular sleep–wake patterns. However we were also able to show different sleep phenotypes within individual participants. It was possible to determine that within the BD group, 23 retained normal sleep–wake patterns with a stable circadian rhythm and total sleep time between 6 h and 10 h. However, 23 had clearly abnormal sleep with striking circadian dysrhythmia in 12 of the patients. Although a number of previous studies have reported different patterns of sleep disturbance in BD, these have usually relied on only short periods of sleep diary or accelerometry data to assess the sleep–wake cycle. Two different studies, each with just 19 BD patients compared group actigraphy variables over periods of 5 and 7 days, respectively, with controls, but did not define different sleep phenotypes between individual BD subjects and simply reported mean activity levels (Millar *et al.* 2004; Jones *et al.* 2005). One problem with the detection of CRD is that patients may appear to have either an insomnia or hypersomnia pattern if the period of recording is too short and this is particularly true of a non-24-h period disorder. The recently revised ICSD-3 diagnostic criteria for this disorder stipulate at least 2 weeks of sleep logs and accelerometry should be performed to make the diagnosis alongside clinical interview (American Academy of Sleep Medicine, 2014). Our data also supports this view given the high rate of patients with subjective descriptions of insomnia (as captured by the HAMD sleep items) while objective accelerometry data showed a low rate of short sleepers. Nine of the 12 patients who had CRD scored the maximum of 2 on at least one of the HAMD sleep items suggesting many of the patients complaining of 'insomnia' actually have CRD.

There is increasing evidence for an intrinsic circadian rhythm dysfunction within a number of psychiatric disorders and some previous studies of melatonin levels in BD patients have shown reduced melatonin compared to controls as well as a later onset, although others have not shown any difference in light suppression response compared to controls (Beck-Friis *et al.* 1984; Souetre *et al.* 1989; Lam *et al.* 1990; Kennedy *et al.* 1996; Nurnberger *et al.* 2000; Robillard *et al.* 2013; Novakova *et al.* 2015). Repeated measurements are required to look at the period to estimate whether it is near 24 h or longer as previous studies have not reported this. In our study, between group comparison of patients and controls showed both reduced melatonin output and a delayed acrophase (time of peak melatonin concentration) within BD compared to controls. However the differences were most marked in those BD patients with abnormal sleep and/or circadian rhythm where total amount of melatonin was significantly lower than BD patients with normal sleep–wake rhythms. There could be a number of potential reasons. Those with fragmented sleep may have abnormal light exposure in rooms with increased light levels or have light on during the night that suppresses melatonin output. Alternatively, a subset of BD patients could have an intrinsic circadian rhythm abnormality although all the controls and the majority of patients with BD had a normal pattern and timing of melatonin secretion, even some with abnormal accelerometry data. Some of those who reported fragmented night sleep had very low melatonin levels of <3 μg/ml and this may provide a mechanistic explanation for the failure to consolidate night sleep for some and this may provide a therapeutic target. We looked for but did not find evidence that mood-stabilizing medication such as lithium affected the circadian rhythm, those on hypnotics had longer sleep time but this might simply reflect the drugs effect.

Overnight respiratory sleep studies analysis showed mild or moderately severe OSA in 29% of patients with BD compared to 10% of controls. There is increasing recognition that secondary consequences of inactivity, weight gain and metabolic syndrome possibly related to medication all increase the risk of conditions such as OSA in those with psychiatric disease. As expected the BD group had an increased BMI compared to the control group. OSA will fragment night sleep and contribute to daytime sleepiness, sedentary behaviour and potentially hypersomnia. Indeed nearly half of the patients with OSA were also rated as long sleepers. Three of the 12 BD patients with OSA were prescribed hypnotics and these patients had a longer mean nocturnal sleep duration (8.9 *v.* 7.7 h) and 24-h sleep duration (11.3 *v.* 9.7 h) than those not prescribed hypnotics. It is possible that undiagnosed OSA may lead to the misdiagnosis of other sleep disorders such as insomnia and lead to inappropriate prescription of hypnotics which may excessively prolong both nocturnal and daytime sleep and may be at least partially responsible for the increased prevalence of long sleepers in this study. While the sample of patients with BD was not an epidemiological one, the prevalence of OSA of 29% in our sample, is consistent with previous research (Kelly *et al.* 2013; Soreca *et al.* 2015) and highlights the need for screening and treatment of OSA in this patient group given the association between OSA and serious cardiovascular morbidity (Butt *et al.* 2010).

Those participants with BD with any cause of abnormal sleep had significantly worse psychosocial functioning and QoL compared to those with normal sleep. The differences between groups remained after covarying for depressed mood suggesting that

https://doi.org/10.1017/S0033291717000186 Published online by Cambridge University Press

accelerometry defined abnormal sleep was associated with lower function and QoL independently of mood. Although we found a moderate correlation between mood and subjective sleep quality measured on the PSQI we found no differences in mood scores between the groups of normal and abnormal BD sleepers. This may be because subjective and objective assessments measure different dimensions of sleep. Other studies have however found associations between disturbed sleep and mood (Eidelman *et al.* 2010; Talbot *et al.* 2012) but both these studies used sleep diaries to assess sleep function whereas in this study we classified normal and abnormal sleep using accelerometry which may account for the difference in findings.

The impact of targeting specific sleep problems therapeutically on the course of BD needs to be examined further. A preliminary randomized controlled trial assessed the effects of cognitive behavioural therapy for insomnia in patients with BD and shown that not only was it possible to improve sleep efficiency and decrease the severity of insomnia, but time in episode of mood disturbance decreased (Harvey *et al.* 2015).

Strengths of the study include a well characterized group, multiple measures of mood and comprehensive measures of sleep and circadian rhythm across 21 days. The use of a triaxial accelerometer that records acceleration in SI units rather than brand-specific activity counts and the fact that the raw accelerometry data was analysed on an open access algorithm meaning future datasets recorded in SI units can use identical analysis methodology thereby making different datasets directly comparable.

Weaknesses of the study include a lack of the gold standard measure of sleep using video polysomnography. However this was a field study and it was felt that studying patients with partial polysomnography in their own homes would increase compliance and the main aim of the home sleep study was to screen for all forms of sleep-disordered breathing. The sample was opportunistic with a potential bias for over-representation of patients with BD and sleep disorders, while controls were screened out if they suffered significant sleep problems. A larger, more representative, sample size would have allowed more accurate assessment of the prevalence of sleep and circadian disorders as well as greater sub group analysis of the differential effect of the different patterns of sleep and circadian rhythm. Future studies might include those with other psychiatric disorders or control subjects with primary sleep disorders to study the impact upon cognition.

In conclusion we have found that many patients with BD that have sleep disorders have CRD and/or OSA. BD participants with abnormal sleep had lower function and QoL which was not accounted for by lower mood. Abnormal sleep in BD is also characterized by reduced 24-h melatonin secretion compared to both healthy controls and those with BD and normal sleep. There is a need for the use of objective markers of the sleep–wake cycle and respiratory function to accurately determine different sleep patterns within clinical populations and assess the impact of specific therapies targeted at these sleep and circadian disorders on long term outcomes of the psychiatric disorders.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717000186.

Acknowledgements

We thank all of the participants for taking part in the study. The study was sponsored by Northumberland, Tyne and Wear NHS Foundation Trust. Some funding to cover running costs was received from Eli Lilly as an unrestricted investigator-initiated and -led award. The design, conduct and analysis of the study was entirely under the control of the authors.

Declaration of Interest

None.

References

Aldhous ME, Arendt J (1988). Radioimmunoassay for 6-sulphatoxymelatonin in urine using an iodinated tracer. *Annals of Clinical Biochemistry* **25**, 298–303.

American Academy of Sleep Medicine (2014). *International Classification of Sleep Disorders*. American Academy of Sleep Medicine: Darien, Illinois.

APA (2000). *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association: Washington, DC.

Beck-Friis J, von Rosen D, Kjellman BF, Ljunggren JG, Wetterberg L (1984). Melatonin in relation to body measures, sex, age, season and the use of drugs in patients with major affective disorders and healthy subjects. *Psychoneuroendocrinology* **9**, 261–277.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

Butt M, Dwivedi G, Khair O, Lip GY (2010). Obstructive sleep apnea and cardiovascular disease. *International Journal of Cardiology* **139**, 7–16.

Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: a new

instrument for psychiatric practice and research. *Psychiatry Research* **28**, 193–213.

Eidelman P, Talbot LS, Gruber J, Harvey AG (2010). Sleep, illness course, and concurrent symptoms in inter-episode bipolar disorder. *Journal of Behavior Therapy and Experimental Psychiatry* **41**, 145–149.

Geoffroy PA, Scott J, Boudebesse C, Lajnef M, Henry C, Leboyer M, Bellivier F, Etain B (2014). Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatrica Scandinavica* **131**, 89–99.

Giglio LM, Magalhaes PV, Andreazza AC, Walz JC, Jakobson L, Rucci P, Rosa AR, Hidalgo MP, Vieta E, Kapczinski F (2009). Development and use of a biological rhythm interview. *Journal of Affective Disorders* **118**, 161–165.

Harvey AG (2008). Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *American Journal of Psychiatry* **165**, 820–829.

Harvey AG, Schmidt DA, Scarna A, Semler CN, Goodwin GM (2005). Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry* **162**, 50–57.

Harvey AG, Soehner AM, Kaplan KA, Hein K, Lee J, Kanady J, Li D, Rabe-Hesketh S, Ketter TA, Neylan TC, Buysse DJ (2015). Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. *Journal of Consulting and Clinical Psychology* **83**, 564–577.

Horne JA, Ostberg O (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology* **4**, 97–110.

Johns MW (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* **14**, 540–545.

Jones SH, Hare DJ, Evershed K (2005). Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disorders* **7**, 176–186.

Kanady JC, Soehnera AM, Harvey AG (2015). A retrospective examination of sleep disturbance across the course of bipolar disorder. *Journal of Sleep Disorders & Therapy* **4**, 214–222.

Kaplan KA, Gruber J, Eidelman P, Talbot LS, Harvey AG (2011). Hypersomnia in inter-episode bipolar disorder: does it have prognostic significance? *Journal of Affective Disorders* **132**, 438–444.

Kelly T, Douglas L, Denmark L, Brasuell G, Lieberman DZ (2013). The high prevalence of obstructive sleep apnea among patients with bipolar disorders. *Journal of Affective Disorders* **151**, 54–58.

Kennedy SH, Kutcher SP, Ralevski E, Brown GM (1996). Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. *Psychiatry Research* **63**, 219–222.

Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman Jr. J, Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Loube DL, Owens J, Pancer JP, Wise M (2005). Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* **28**, 499–521.

Lam RW, Berkowitz AL, Berga SL, Clark CM, Kripke DF, Gillin JC (1990). Melatonin suppression in bipolar and unipolar mood disorders. *Psychiatry Research* **33**, 129–134.

Michalak EE, Murray G (2010). Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. *Bipolar Disorders* **12**, 727–740.

Millar A, Espie CA, Scott J (2004). The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. *Journal of Affective Disorders* **80**, 145–153.

Minors DS, Waterhouse JM (1988). Mathematical and statistical analysis of circadian rhythms. *Psychoneuroendocrinology* **13**, 443–464.

Nelson HE (1982). *National Adult Reading Test (NART): Test Manual*. NEFR-Nelson: Windsor.

Ng TH, Chung KF, Ho FY, Yeung WF, Yung KP, Lam TH (2015). Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: a systematic review and meta-analysis. *Sleep Medicine Reviews* **20**, 46–58.

Novakova M, Prasko J, Latalova K, Sladek M, Sumova A (2015). The circadian system of patients with bipolar disorder differs in episodes of mania and depression. *Bipolar Disorders* **17**, 303–314.

Nurnberger Jr. JI, Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, Miller A, Bowman ES, Miller MJ, Rau L, Smiley C, Davis-Singh D (2000). Melatonin suppression by light in euthymic bipolar and unipolar patients. *Archives of General Psychiatry* **57**, 572–579.

Robillard R, Naismith SL, Rogers NL, Scott EM, Ip TK, Hermens DF, Hickie IB (2013). Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *European Psychiatry* **28**, 412–416.

Rosa AR, Sanchez-Moreno J, Martinez-Aran A, Salamero M, Torrent C, Reinares M, Comes M, Colom F, Van Riel W, Ayuso-Mateos JL, Kapczinski F, Vieta E (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice & Epidemiology in Mental Health* **3**, 5.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59** (Suppl. 20), 22–33; quiz 34–57.

Soreca I, Buttenfield JA, Hall MH, Kupfer DJ (2015). Screening for obstructive sleep apnea in patients with bipolar I disorder: comparison between subjective and objective measures. *Bipolar Disorders* **17**, 345–348.

Souetre E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B, Ardisson JL, Darcourt G (1989). Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Research* **28**, 263–278.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983). *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press: Palo Alto, CA.

Talbot LS, Stone S, Gruber J, Hairston IS, Eidelman P, Harvey AG (2012). A test of the bidirectional association

between sleep and mood in bipolar disorder and insomnia. *Journal of Abnormal Psychology* **121**, 39–50.

te Lindert BH, Van Someren EJ (2013). Sleep estimates using microelectromechanical systems (MEMS). *Sleep* **36**, 781–789.

van Hees VT, Sabia S, Anderson KN, Denton SJ, Oliver J, Catt M, Abell JG, Kivimaki M, Trenell MI, Singh-Manoux A (2015). A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. *PLoS ONE* **10**, e0142533.

Van Someren EJ, Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB (1999). Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiology International* **16**, 505–518.

Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C (2003). Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Medicine* **4**, 121–132.

Williams JB, Kobak KA, Bech P, Engelhardt N, Evans K, Lipsitz J, Olin J, Pearson J, Kalali A (2008). The GRID-HAMD: standardization of the hamilton depression rating scale. *International Clinical Psychopharmacology* **23**, 120–129.

Wulff K, Joyce E, Middleton B, Dijk DJ, Foster RG (2006). The suitability of actigraphy, diary data, and urinary melatonin profiles for quantitative assessment of sleep disturbances in schizophrenia: a case report. *Chronobiology International* **23**, 485–495.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* **133**, 429–435.