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Research report

Sleep in remitted bipolar disorder: A naturalistic case-control study using actigraphy

Pierre Alexis Geoffroy [a,c,d,e,*], Carole Boudebesse [a,c,e], Frank Bellivier [e,f,g], Mohamed Lajnef [a], Chantal Henry [a,b,c,e], Marion Leboyer [a,b,c,e], Jan Scott [h,i], Bruno Etain [a,c,e]

[a] INSERM, U955, Psychiatrie génétique, Créteil 94000, France
[b] Université Paris Est, Faculté de médecine, Créteil 94000, France
[c] AP-HP, Hôpital H. Mondor – A. Chenevier, Pôle de Psychiatrie, Créteil 94000, France
[d] Pôle de psychiatrie, Université Lille Nord de France, CHRU de Lille, F-59000 Lille, France
[e] Fondation FondaMental, Créteil 94000, France
[f] AP-HP, GH Saint-Louis, Lariboisière, Fernand Widal, Pôle Neurosciences, Paris, France
[g] Université Paris-7 Paris-Diderot, UFR de Médecine, Paris, France
[h] Academic Psychiatry, Institute of Neuroscience, Newcastle University, UK
[i] Centre for Affective Disorders, Institute of Psychiatry, London, UK

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ABSTRACT

Introduction: Findings from actigraphic studies suggesting that sleep and circadian rhythms are disrupted in bipolar disorder (BD) patients have been undermined by methodological heterogeneity and the failure to adequately address potential confounders.
Method: Twenty-six euthymic BD cases and 29 healthy controls (HC), recruited from University Paris-Est and matched for age and gender, were compared on subjective (Pittsburgh Sleep Questionnaire Inventory; PQSI) and objective (mean scores and variability in actigraphy) measures of sleep as recorded by over 21 consecutive days.
Results: Multivariate generalized linear modelling (GLM) revealed significant differences between BD cases and HC for five PSQI items (total score and four subscales), four actigraphy variables (mean scores) and five actigraphy variability measures. Backward stepwise linear regression (BSLR) indicated that a combination of four variables (mean sleep duration, mean sleep latency, variability of the fragmentation index over 21 days, and mean score on PSQI daytime dysfunction sub-scale) correctly classified 89% of study participants as cases or controls (Chi-square = 39.81; $df = 6$; $p = 0.001$).
Limitations: The sample size (although larger than most actigraphy studies) and incomplete matching of cases and controls may have influenced our findings. It was not possible to control for potential effects of psychotropic medication or differences in employment status between groups.
Conclusions: When potential confounders of sleep and circadian profiles are adequately taken into account (particularly age, gender, daytime sleepiness, mood symptoms, body mass index, and risk of sleep apnoea), a selected subset of quantitative (mean scores) and qualitative (variability) features differentiated euthymic BD cases from HC.

1. Introduction

Bipolar disorder (BD) is a severe mental disorder and the worldwide prevalence of the BD spectrum is 1–4%. Although researchers agree that BD is multifactorial with inherited, genetic and environmental risk factors, the patho-physiological determinants are unknown (Geoffroy et al., 2013). Recent studies of circadian genes and phenotypes indicate that sleep/activity dysregulation is a plausible model for BD episode recurrence (McClung, 2013). Abnormalities in sleep and circadian biomarkers during the euthymic phase have been identified, revealing that this dysregulation is not purely an epiphenomenon of acute illness episodes; indeed, increased disruption of the sleep homoeostasis and circadian system are frequently associated with relapse (Etain et al., 2011; Harvey, 2008). Consequently, the validation of sleep and circadian biomarkers of BD may help in the development of both methods for earlier and more accurate detection of unstable mental states, and of novel strategies to prevent relapse (Frey et al., 2013).

Subjective reporting of sleep profiles is useful in clinical practice, although objective measures are increasingly utilized for research.

* Corresponding author at: Pôle de Psychiatrie des Hopitaux Universitaires Henri Mondor, Centre Expert Bipolaire, Hôpital Albert Chenevier, pavillon Hartman, 40 rue de Mesly, 94000 Créteil Cedex, France. Tel.: +33 1 49 81 32 90; fax: +33 1 49 81 30 99.
E-mail address: pierre.a.geoffroy@gmail.com (P.A. Geoffroy).

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Actigraphy (recording the subject's sleep/wake cycles generally with a mobile portable device) is considered to be the most relevant non-invasive technique for the measurement of sleep/wake irregularities (Morgenthaler et al., 2007). Actigraphy has been used extensively in the field of chronobiology, and has more recently been applied to research in mood disorders, and in particular the characterization of sleep homoeostasis and circadian rhythm abnormalities in BD (Kaplan et al., 2012). We identified nine published actigraphic studies of BD: although most suggest that, even in remission, BD cases were more likely than 'controls' to display a range of sleep abnormalities, there was significant heterogeneity in the methodologies employed (Gershon et al., 2012; Harvey et al., 2005; Jones et al., 2005; Kaplan et al., 2012; Millar et al., 2004; Mullin et al., 2011; Ritter et al., 2012; Salvatore et al., 2008; St-Amand et al., 2012). The five major between-study differences were (1) the mean age of sample (e.g. ranging from adolescents with early onset BD to older adults with chronic, persistent BD); (2) the overall sample size (the total number of participants including cases and controls ranging from 27 to 68); (3) the duration of actigraphic recording (some studies recorded data for only 3 days with a median of 6 days for the nine studies); (4) different approaches to 'matching' cases and controls, with a number of studies failing to match on demographic characteristics; and/or (5) failure to control for confounding factors such as body mass index (BMI) and/or sleep apnoea syndrome (SAS).

Most of these previous studies examined 'quantitative' differences (mean scores of each sleep measure for each group), and mainly focused on four basic sleep variables (sleep duration, latency and efficiency, and waking after sleep onset). However, it is increasingly argued that differences in terms of quality or variability (which can be represented by the standard deviations [SD] in the mean scores for a particular measure extracted from actigraphic recordings) may be more sensitive markers for distinguishing BD sleep patterns from those of controls (Scott, 2011). Only three studies have published data relevant to this approach (Gershon et al., 2012; Millar et al., 2004; Mullin et al., 2011), but comparing the findings is difficult. Indeed, the study among adolescents (Mullin et al., 2011), and the study involving three days of actigraphic recording (Salvatore et al., 2008) differed from the study in older adults over a longer period (28 days) of actigraphic monitoring (Gershon et al., 2012). Also, none of these studies controlled for the possible effects of BMI or level of risk for SAS on sleep profiles. Thus, published findings for the quality and quantity of sleep in remitted BD may have been confounded by other individual characteristics, including those known to affect sleep directly, and by heterogeneity in sampling and/or in study design.

To overcome the limitations noted in previous studies, we report an analysis of mean scores of subjective and objective measures, and variability in objective measures, using methodological approaches designed to avoid potential confounders. Previous studies examined each reported sleep variable in independent analyses and none of them adequately addressed potential confounders in their statistical analytic strategy. We therefore tried to overcome some of these previous weaknesses in design by examining which combination of sleep measures best distinguishes cases from controls. Our hypothesis was to identify and/or confirm reliable and robust circadian/sleep markers differentiating euthymic BD cases from HC when potential confounders of sleep and circadian differences are taken into account (most notably, age, gender, daytime sleepiness, mood symptoms, BMI and risk of sleep apnoea).

2. Materials and methods

2.1. Sample

With ethical approval from the Institutional review board, written informed consent was obtained from 55 adults (BD=26; HC=29). The included cases were recruited from our university-affiliated psychiatric clinic (University Paris Est) and the HC were recruited from individuals attending the blood donor service at the adjacent general hospital (Henri Mondor Hospital, Creteil).

The groups (BD and HC) were matched as closely as possible for age and gender: perfect matching was not feasible, so we increased the size of the HC group to ensure that we had a control of the same age and/or a control of the same gender for each case recruited. Individuals eligible for the study were included if, during the preceding three months, they had (1) not experienced any periods of severe sleep disruption due to somatic conditions (e.g. organic insomnia/hypersomnia or sleep-wake disorders) and/or any life event that may have altered their sleep patterns (e.g. shift work, jet-lag, child birth, trauma, or somatic disease known to be associated with sleep disturbances); (2) *not* been hospitalised or received a treatment that may disrupt sleep (*e.g.* for cases: electro-convulsive therapy); (3) not been prescribed medication or taken drugs that may disrupt sleep (e.g. sympathomimetic stimulants, corticosteroids, thyroid hormones, antiarrhythmics, beta-blockers, clonidine, diuretics, theophylline, and medications containing alcohol or caffeine) and not changed either the dose or type of psychotropic treatment.

Bipolar cases also had to fulfil the following inclusion criteria: the DSM-IV criteria for BD according to the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1988); currently euthymic i.e. they scored <8 on both the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) and the Young Manic Rating Scale (YMRS; Young et al., 1978); and the International Society of Bipolar Disorder task force criteria (Tohen et al., 2009) for remission (i.e. they had not experienced a BD episode in the prior three months). Patients experiencing a BD relapse whilst participating in the study were excluded.

Controls were assessed with the DIGS and the Family Interview for Genetic Studies (Maxwell, 1992); individuals were excluded if they had any personal history of DSM-IV disorders and family history of schizophrenia, affective disorders and/or suicide attempts.

2.2. Assessment procedures

Cases and controls were first assessed for affective symptoms using the MADRS and YMRS, and their BMI was calculated. Participants then completed the Berlin Questionnaire (a measure of the risk of SAS) (Netzer et al., 1999), and the Epworth Sleepiness Scale (a measure daytime sleepiness) (Johns, 1991), to allow these potential confounding factors to be taken into account.

2.2.1. Self-ratings of sleep profile

All participants recorded their subjective sleep quality using the French version of the 19-item Pittsburgh Sleep Quality Index (PSQI) (Blais et al., 1997). Here, we report the mean total score over 21 consecutive days and seven other specific measures of sleep (with higher scores indicating lower quality or worse outcome): sleep quality, latency, duration and efficiency, disturbances, use of sleeping medication and daytime dysfunction (*e.g.* sleepiness and enthusiasm).

2.2.2. Actigraphy

All participants were asked to wear an actigraph (AW-7 CamNtech) on the wrist of their non-dominant hand for the 21 consecutive days, the days for which they completed the PSQI self-ratings. The AW-7 actigraph is an accelerometer that detects the intensity and the amount of movement as a function of time. For this study, data were sampled in one-minute epochs and participants were instructed to press the event-marker when they went

to bed to go to sleep and when they got out of bed at the start of the next day. They also completed a sleep diary for these 21 days. Other requirements were kept to a minimum to try to minimise intrusion into sleep/activity routines. Recording was made during periods when the participants were not on vacation and not involved in unusual activities.

Two experienced psychiatrists (PAG and CB) analysed the actigraphic records of cases and controls using the sleep detection algorithm provided by Actiwatch software (Actiwatch Activity & Sleep Analysis Ltd CamNtech® 7.28) and any incongruences between the sleep diary and actigraphy rest periods were clarified prior to statistical analyses (see Boudebesse et al., 2012 for details).

We selected the ten clinically interpretable actigraphic measures that have been most frequently reported in previous studies (Gershon et al., 2012; Harvey et al., 2005; Jones et al., 2005; Kaplan et al., 2012; Millar et al., 2004; Mullin et al., 2011; Ritter et al., 2012; Salvatore et al., 2008; St-Amand et al., 2012). There were six measures of basic sleep profile: time in bed, sleep duration, sleep latency, wake after sleep onset (WASO), sleep efficiency, fragmentation index (a measure of sleep continuity); two measures of activity during sleep: mean activity in active periods of sleep, mean sleep activity; and two measures of variability: inter-daily stability and intra-daily variability. To facilitate comparison with other studies that used different measures of variability, we also estimated the variability of the basic sleep measures over 21 days (using standard deviations (SD) of the mean scores) (see Millar et al., 2004; Mullin et al., 2011 for the rationale and details of this approach).

2.3. Statistical analysis

All analyses were performed using SPSS 19.0. We included several covariates in the analysis: age and/or gender because matching was incomplete, and also BMI, SAS, daytime sleepiness (Epworth) and the presence of residual or low-grade mood symptoms (as measured using the MADRS or YMRS) that can all be associated with differences in sleep profile independently of case-control group status (*i.e.* BD or HC). We undertook a power calculation to assess the sample size required to detect a between-group Effect Size (ES) of ≥ 0.35 (classified as a medium ES according to Cohen (1977) for self-rated and objective measures of sleep whilst controlling for these potential confounders. We thereby estimated that the sample size of 55 individuals had $>80\%$ power to detect differences at a significance level of 0.05 (and an ES ≥ 0.35) in a multivariate analysis.

The analysis involved three stages. First, we checked the normality of the distributions of variables and undertook log transformation if required (none were needed). Second, we used multivariate Generalized Linear Modelling (GLM) for the analysis of sleep variables (self-ratings; actigraphy measures). GLM is a flexible statistical model that incorporates normally distributed dependent variables and categorical or continuous independent variables (we also report Wilk's Lambda, to indicate the proportion of generalized variance in the dependent variables explained by the model and also to give the best estimate of overall power of the analysis to differentiate between groups). We used bootstrapping (*i.e.* resampling) to reduce biases introduced by any 'outliers' and to obtain the best estimates of summary statistics. Any variables that were significantly different between groups (even allowing for interactions between group and other categorical or continuous variables) were then entered into a Backward Stepwise Logistic Regression (BSLR) to assess the *combination* of these selected variables that *best* classified individuals as cases or controls. The proportion of cases correctly classified is reported along with the odds ratios (OR) and 95% confidence intervals (95% CI) for each variable included in the final optimal model.

3. Results

3.1. Socio-demographic and clinical characteristics

The sample is composed of 55 individuals (26 BD cases; 29 HC), the mean age was about 54 years and more than half (30/55) were female (Table 1). Cases fulfilled the criteria for BD subtype I ($n=16$) or BD subtype II ($n=10$). One patient did not receive medication, and nine patients received only one psychotropic medication and 16 received ≥ 2 medications. The psychotropic treatments used were lithium ($n=12$), anti-convulsants ($n=15$), atypical antipsychotics ($n=7$), typical antipsychotics ($n=4$), benzodiazepines ($n=4$), antidepressants ($n=5$).

There were no statistically significant differences between the groups for age, gender, BMI, level of risk of SAS, or daytime sleepiness. Levels of mood symptoms were very low in both groups, but the median score on the MADRS was slightly higher for the BD group than controls (0.50 vs. 0.00); there were no between-group differences on the YMRS.

3.2. Subjective and objective measures of sleep

Mean scores for a number of subjective and objective ratings of sleep differed between cases and controls. There were statistically significant differences between the groups for several PSQI and actigraphy measures, even when taking into account gender, risk of SAS, age, BMI, and scores on the Epworth, MADRS, and YMRS. When considering the multivariate values for the model as a whole, there was a significant difference between the patients with BD and HC (Wilks' lambda, $F=90.89$; *df* 26,16; $p=0.0001$; statistical power, 0.93).

Several interactions between group and other variables were identified; in particular, five PSQI items (Total score and scores for PSQI subscales 1, 4, 5 and 7), four mean actigraphy measures (sleep latency, duration, efficacy, and fragmentation index, inter-daily stability) and five actigraphy variability measures (variability in sleep duration, sleep efficiency, fragmentation index and time in bed) differed between the groups (Table 2). As measured by the PSQI, patients with BD were more likely to report poorer sleep quality ($p=0.001$), poorer sleep efficiency ($p=0.001$), more frequent sleep disturbances ($p=0.001$), and more daytime dysfunction ($p=0.001$); consequently they had poorer global sleep quality as measured by the PSQI total score ($p=0.0001$). As determined from mean actigraphy scores, patients with BD were more likely to have longer sleep latency

Table 1
Baseline characteristics of bipolar disorder (BD) cases and healthy controls (HC).

Baseline characteristics	BD ($n=26$) Mean ($\pm$SD)	HC ($n=29$) Mean ($\pm$SD)	*p*
Age (years)	53.50 ($\pm$11.49)	54.10 ($\pm$9.11)	0.78
Montgomery–Asberg Depression rating scale	1.85 ($\pm$2.80)	0.48 ($\pm$1.35)	0.02
Median score	0.50	0.00	
Young mania rating Scale	0.65 ($\pm$1.38)	0.14 ($\pm$0.44)	0.16
Median score	0.00	0.00	
Body mass index	26.74 ($\pm$5.72)	26.64 ($\pm$4.17)	0.68
Daytime sleepiness[b]	8.85 ($\pm$3.90)	6.86 ($\pm$3.72)	0.12
	***n* (%)**	***n* (%)**	
Sleep apnoea syndrome[a]			0.09
High risk category	6 (23%)	2 (7%)	
Low risk category	20 (77%)	27 (93%)	
Gender distribution			0.13
Female	17 (65%)	13 (45%)	
Male	9 (35%)	16 (55%)	

[a] Risk of sleep apnoea syndrome assessed using the Berlin Questionnaire.
[b] Daytime sleepiness assessed using the Epworth Sleepiness Scale.

Table 2
Differences between sleep measures for cases (BD) and controls (HC).

Sleep measures	BD ($n=26$)	HC ($n=29$)	*Multivariate generalized linear model*[a]		
	Mean (±SD)	Mean (±SD)	*F*	*p*	Observed power
PSQI measures					
Total score	7.38 (±3.49)	4.11 (±2.13)	4.45	**0.0001**	0.99
Sub-scale 1	1.19	0.71	3.64	**0.001**	0.99
Subjective sleep quality	(±0.69)	(±0.66)			
Sub-scale 2	1.19	0.82	0.70	0.74	0.33
Sleep latency	(±0.80)	(±0.91)			
Sub-scale 3	0.62	0.50	1.53	0.15	0.70
Sleep duration	(±0.94)	(±0.75)			
Sub-scale 4	0.88	0.43	3.86	**0.001**	0.99
Habitual sleep efficiency	(±0.95)	(±0.69)			
Sub-scale 5	1.58	1.18	3.67	**0.001**	0.99
Sleep disturbances	(±0.58)	(±0.48)			
Sub-scale 6	0.69	0.14	1.08	0.18	0.68
Use of night sedation	(±1.09)	(±0.59)			
Sub-scale 7	1.23	0.32	3.53	**0.001**	0.98
Daytime dysfunction	(±0.99)	(±0.48)			
Mean actigraphy scores					
Time in bed (min)	511.81 (±50.28)	482.31 (±49.36)	1.79	0.08	0.79
Sleep duration (min)	475.42 (±64.5)	455.83 (±53.98)	2.38	**0.019**	0.91
Sleep latency (min)	25.23 (±33.65)	11.59 (±7.98)	2.81	**0.007**	0.95
Wake after sleep onset (min)	57.88 (±23.17)	52.62 (±27.33)	0.57	0.85	0.27
Sleep efficiency (%)	81.54 (±9.87)	84.90 (±6.32)	2.13	**0.036**	0.86
Fragmentation index	32.04 (±10.51)	28.69 (±10.88)	2.01	**0.05**	0.84
Mean activity in active sleep periods[b]	115.54 (±37.67)	91.10 (±24.39)	1.21	0.31	0.58
Mean overall sleep activity	19.35 (±13.10)	12.69 (±7.07)	1.69	0.11	0.76
Inter-daily stability	0.503 (±0.14)	0.512 (±0.12)	2.17	**0.033**	0.87
Intra-daily variability	0.82 (±0.17)	0.80 (±0.18)	0.90	0.56	0.43
Actigraphy measure variability over 21 days					
Time in bed (min)	1.44 (±0.7)	1.33 (±0.5)	2.97	**0.005**	0.96
Sleep duration (min)	1.3 (±0.6)	1.13 (±0.4)	2.08	**0.04**	0.86
Sleep latency (min)	0.67 (±1.2)	0.43 (±0.7)	1.40	0.21	0.66
Wake after sleep onset (min)	0.49 (±0.3)	0.36 (±0.3)	1.80	0.08	0.79
Sleep efficiency (%)	8.77 (±7.5)	6.13 (±3.8)	2.26	**0.026**	0.89
Fragmentation index	12.52 (±7.3)	9.28 (±2.7)	2.16	**0.033**	0.96

[a] Model controlled for age, gender, daytime sleepiness (Epworth), current mood symptoms (MADRS and YMRS), BMI and risk of sleep apnoea (Berlin).
[b] Intensity of movement during periods of sleep when activity occurs.

Table 3
Backward Stepwise Logistic Regression (BSLR) showing (a) the best combination of variables for correctly classifying study participants as cases or controls and (b) the overall classification rate by group.

Variable			95% C.I.	
	p	Odds Ratio	Lower	Upper
(a) Variables included in the final BSLR model				
Sleep duration	0.015	1.03	1.01	1.05
Sleep latency	0.012	1.24	1.05	1.47
Fragmentation index: mean variability	0.01	1.63	1.12	2.31
Daytime dysfunction (PSQI subscale-7)	0.005	8.35	2.50	18.11

Observed	Predicted		
	Controls	Cases	% Correctly classified
(b) Classification table and summary statistics			
Controls[a]	25	3	89.3
Cases	3	23	88.5

% of all participants correctly classified 89%.
Chi-square 39.81 (*df* 6) $p=0.001$.

[a] One control participant was excluded from the analysis due to inadequate data.

($p=0.007$), longer sleep duration ($p=0.02$), poorer sleep efficiency ($p=0.04$), higher fragmentation index ($p=0.05$) and poorer inter-daily stability ($p=0.03$). For actigraphy variability over 21 days, patients with BD were more likely to show more variable time in bed ($p=0.005$), sleep duration ($p=0.04$), sleep efficiency ($p=0.03$) and fragmentation index ($p=0.03$).

3.3. Regression analysis

We next used BSLR to determine the optimal combination of variables that best classified participants as cases or controls. When the variables identified by the GLM were entered into a BSLR; a combination of four variables (mean sleep duration, mean sleep latency, variability in fragmentation index over 21 days, and mean score on PSQI sub-scale 7: daytime dysfunction) correctly classified 89% of the study participants as cases or controls (Chi-square = 39.81; $df = 6$; $p = 0.001$). The OR for these variables ranged from 1.03 (sleep duration) to 8.35 (PSQI 'daytime dysfunction' sub-scale) (Table 3). However, whilst daytime dysfunction is the variable with the highest OR, on its own it classified about 75% cases, so the other measures significantly contributed to the improved classification obtained by the final model.

4. Discussion

We report a study of sleep abnormalities in remitted bipolar (BD) patients compared with HC that also controlled for major potential confounders, and replicate and extend previous findings. In particular, objective and subjective assessments of sleep indicate that, compared to controls, BD patients show longer sleep duration, longer sleep latency, poorer sleep efficiency, higher fragmentation index (with actigraphy) (Gershon et al., 2012; Harvey et al., 2005; Jones et al., 2005; Kaplan et al., 2012; Millar et al., 2004; Mullin et al., 2011; Ritter et al., 2012; Salvatore et al., 2008; St-Amand et al., 2012), lower sleep quality, weaker sleep efficiency, more sleep disturbances, and more daytime dysfunction (with PSQI) (Rocha et al., 2013). The partial discrepancy between PSQI (subjective measure) and actigraphy (objective measure) findings has also been observed previously: patients with BD underestimated their sleep latency and duration on questionnaire assessments compared to actigraphy examination. This may arise as a consequence of misperceptions in patients with BD regarding their sleep quality (Gershon et al., 2012; Harvey et al., 2005; Millar et al., 2004). Nevertheless, actigraphy demonstrated a high correlation with polysomnography (PSG) measures in patients with BD regarding sleep latency, sleep duration, fragmentation index and sleep efficiency, which further validate our findings (Kaplan et al., 2012).

We report several new findings for issues that have been under-explored: patients with BD presented with more variability for time in bed, sleep duration, sleep efficiency and fragmentation index. Indeed, sleep duration, sleep efficiency and fragmentation index are altered not only in quantity (mean) but also in variability (SD) in BD patients. This indicates that analyses of actigraphic markers should not be restricted to classical sleep markers (latency, duration, efficiency and WASO), but should also be extended to the variability of markers. Indeed, Millar et al. (2004) were the first to explore the variability of markers in different groups and showed that the means of none of the four actigraphic measures differed between cases and controls, but variability of two of the four measures did (sleep duration and night waking time) with an effect size around 0.35. Similarly, Gershon et al. (2012) confirmed more variability of both time in bed and sleep duration for BD patients than controls (although the latter did not survive their Bonferroni's correction) Millar et al. (2004) also found more variability of night wake time among remitted cases. Both Gershon et al. (2012) and our study (0.40 ± 0.3 vs. 0.36 ± 0.3) replicate this finding. Further, we observed significant variability of sleep efficiency and fragmentation index, which confirmed the greater variability of sleep patterns and circadian rhythms in patients with remitted BD than controls. Mullin et al. (2011), despite also assessing the variability of actigraphic measures, did not find any significant differences; however, that study involved recordings for only four nights, which may have been too short to detect variability. Studies involving sufficient duration of recording would be useful to explore further the variability of actigraphic measures in BD patients, and to examine trait-markers of BD.

The results of our regression analysis deserve comment. The fact that 89.3% of BD and 88.5% of HC could be correctly classified indicates that a combination of different methods of assessment (i.e. PSQI, mean and SD actigraphy measures) may serve as a useful marker of BD. Daytime dysfunction, sleep duration, sleep latency and fragmentation index variability appeared, when combined, to identify clear circadian biomarkers of remitted BD. Indeed, it may be possible to define a biosignature of BD using these four features. We partially replicate the findings of Millar et al. (2004) whose best multivariate model involved a combination of one actigraphic (variability of sleep duration) and two subjective sleep variables (average sleep duration, and average onset latency). These two studies indicate that individuals are best classified by a combination of subjective and objective measures (quantity and variability). The other comment is that it is noteworthy that – although daytime dysfunction – was a sub-scale score of the PSQI, it is debatable whether this is a specific measure of sleep pattern/dysfunction. Indeed in BD cases it may be a measure of overall effects of illness or possible effects of medication, not only of daytime consequences of disturbed sleep.

Our study has some limitations. Controlling for psychotropic medications is always difficult in bipolar disorder research. In this study, the size of the case sub-group did not allow us to include treatment data as a covariate in any 'within group' sub-analyses. However, the type and dose of psychotropic medications have been found to be unrelated to actigraphic measures in patients with remitted BD (Salvatore et al., 2008). Moreover, we believe that on balance, it can be hypothesized that medication would be as likely or more likely to improve the patients' quality of sleep as to have a detrimental effect. We also attempted to control for daytime sedation by using scores on the Epworth scale as a covariate in the preliminary between group comparisons. As such, the observed differences between cases and controls may have been attenuated rather than exaggerated by such treatments. Indeed, antipsychotics, valproate and lithium have been shown to regulate sleep and circadian rhythms in patients with bipolar disorder (Geddes and Miklowitz, 2013). Therefore, we believe that it is unlikely that psychotropic drugs had a major influence. Our sample size is small; however, it is of reasonable size for an actigraphic study and larger than the median for the previous studies cited (median = 40) (Gershon et al., 2012; Harvey et al., 2005; Jones et al., 2005; Kaplan et al., 2012; Millar et al., 2004; Mullin et al., 2011; Ritter et al., 2012; Salvatore et al., 2008; St-Amand et al., 2012). We studied several markers of subjective and objective sleep. Although GLM is an appropriate method for assessing multiple, potentially inter-dependent measures, and the power calculation (and estimated effect sizes) suggest we have reduced the risk of type II error, it is clear that it would be beneficial to use a larger sample for further studies. Nevertheless, our study allowed controlling for confounding factors that were insufficiently taken into account in previous studies; our greater attention to potential confounding factors was an important methodological strength relative to most previous studies.

We were thus able to confirm that patients with BD in remission experienced substantial sleep disturbances that can be measured both objectively and subjectively. This provides further evidence of the involvement of sleep and circadian rhythm abnormalities in the pathophysiology of BD, as proposed by, e.g., Harvey et al. (Harvey, 2008). Indeed, genetic variants of candidate genes (mainly circadian genes) may predispose individuals to be

relatively less able to adapt their circadian rhythms appropriately to their environment, and therefore to greater vulnerability to sleep disturbances. Since circadian and neurotransmission systems are highly connected, circadian and/or sleep-related abnormalities may affect the functioning of the dopamine and serotonin circuitry, which in turn may affect mood regulation. These chronic sleep and circadian rhythm disturbances (observable in acute episodes and in remission) may thereby contribute to the more general issues persistently encountered bipolar patients such as poor quality of cognitive functioning, residual emotional hyper-reactivity or vulnerability to metabolic disturbances (Boland et al., 2012; Boudebesse and Henry, 2012; McClung, 2013; Soreca et al., 2012).

The findings we report have several important clinical implications. Sleep and circadian rhythm disturbances in remitted BD might be treatable by manipulating the circadian system using chronobiological medication (*e.g.* melatonin or melatonin analogues) or sleep focused psychological interventions (Kaplan and Harvey, 2013; Livianos et al., 2012; Pacchierotti et al., 2001; St-Amand et al., 2012). Attention to rhythm abnormalities is of particular interest because biological rhythm dysfunctions have been found to be associated to a wide range of sources of poor functioning and are the earliest markers of impending mood relapses (Giglio et al., 2010). Thus, better identification of these abnormalities in clinical practice might facilitate the prevention of the evolution of prodromes of mood relapses, and also help improve functioning in inter-episodic BD. It may allow a more complete approach including combinations of treatments acting on several dimensions including sleep or circadian disturbances (Geoffroy et al., 2012). These findings more generally indicate a new area for research both into possible therapeutic targets and to improve our understanding of the circadian pathophysiology of BD.

5. Conclusion

This 21-day case-control study demonstrates the presence of subjective and objective disturbances of sleep and activity markers in patients with BD during remission. Disturbances identified by actigraphy are both quantitative (mean scores) and qualitative (variability). We further confirm the greater variability in sleep markers in remitted patients with BD. These findings indicate that future studies should examine both the mean scores and the variability over extended periods of time. In addition, we show that a combination of subjective and objective measures (quantity and variability) may be a better circadian biosignature of BD than any single measure on its own.

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Conflict of interest

PA Geoffroy has received a prize from Bayer for being Laureate of the Medical University of Lille.

C. Boudebesse has received a research bursary from Laboratoires Servier; a prize for her thesis in medicine from Sanofi-Aventis; and honoraria from Ostuka as an independent symposium speaker.

B. Etain and F. Bellivier have received honoraria and financial compensation as independent symposium speakers from Sanofi-Aventis, Lundbeck, AstraZeneca, Eli Lilly, Bristol-Myers Squibb and Servier.

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J. Scott has received funding to attend national and international conferences, financial compensation as an independent symposium speaker for talks on early onset in BD and psychosocial aspects of BD, and advisory board fees from AstraZeneca, BMS-Otsuka, Eli Lilly, GSK, Jansen-Cilag, Lundbeck, Sanofi-Aventis and Servier.

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References

Blais, F.C., Gendron, L., Mimeault, V., Morin, C.M., 1997. Evaluation of insomnia: validity of 3 questionnaires. Encephale 23, 447–453.
Boland, E.M., Bender, R.E., Alloy, L.B., Conner, B.T., Labelle, D.R., Abramson, L.Y., 2012. Life events and social rhythms in bipolar spectrum disorders: an examination of social rhythm sensitivity. J. Affect. Disord. 39, 264–272.
Boudebesse, C., Henry, C., 2012. [Emotional hyper-reactivity and sleep disturbances in remitted patients with bipolar disorders]. Encephale 38 (4), S173–S178.
Boudebesse, C., Leboyer, M., Begley, A., Wood, A., Miewald, J., Hall, M., Frank, E., Kupfer, D., Germain, A., 2012. Comparison of five actigraphy scoring methods with bipolar disorder. Behav. Sleep. Med. 11, 275–282.
Cohen, J., 1977. Statistical Power Analysis for the Behavioral Sciences, 2nd edition Academic Press, New-York, NY.
Etain, B., Milhiet, V., Bellivier, F., Leboyer, M., 2011. Genetics of circadian rhythms and mood spectrum disorders. Eur. Neuropsychopharmacol. 21 (4), S676–S682.
Frey, B.N., Andreazza, A.C., Houenou, J., Jamain, S., Goldstein, B.I., Frye, M.A., Leboyer, M., Berk, M., Malhi, G.S., Lopez-Jaramillo, C., Taylor, V.H., Dodd, S., Frangou, S., Hall, G.B., Fernandes, B.S., Kauer-Sant'Anna, M., Yatham, L.N., Kapczinski, F., Young, L.T., 2013. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust. N. Z. J. Psychiatry 47, 321–332.
Geddes, J.R., Miklowitz, D.J., 2013. Treatment of bipolar disorder. Lancet 381, 1672–1682.
Geoffroy, P.A., Etain, B., Henry, C., Bellivier, F., 2012. Combination therapy for manic phases: a critical review of a common practice. CNS Neurosci. Ther. 18, 957–964.
Geoffroy, P.A., Etain, B., Scott, J., Henry, C., Jamain, S., Leboyer, M., Bellivier, F., 2013. Reconsideration of bipolar disorder as a developmental disorder: importance of the time of onset. J. Physiol. Paris 07, 278–285.
Gershon, A., Thompson, W.K., Eidelman, P., McGlinchey, E.L., Kaplan, K.A., Harvey, A.G., 2012. Restless pillow, ruffled mind: sleep and affect coupling in interepisode bipolar disorder. J. Abnorm. Psychol. 121, 863–873.
Giglio, L.M., Magalhães, P.V.S., Kapczinski, N.S., Walz, J.C., Kapczinski, F., 2010. Functional impact of biological rhythm disturbance in bipolar disorder. J. Psychiatr. Res. 44, 220–223.
Harvey, A.G., 2008. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am. J. Psychiatry 165, 820–829.
Harvey, A.G., Schmidt, D.A., Scarnà, A., Semler, C.N., Goodwin, G.M., 2005. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. Am. J. Psychiatry 162, 50–57.
Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14, 540–545.
Jones, S.H., Hare, D.J., Evershed, K., 2005. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. Bipolar Disord. 7, 176–186.
Kaplan, K.A., Harvey, A.G., 2013. Behavioral treatment of insomnia in bipolar disorder. Am. J. Psychiatry 170, 716–720.
Kaplan, K.A., Talbot, L.S., Gruber, J., Harvey, A.G., 2012. Evaluating sleep in bipolar disorder: comparison between actigraphy, polysomnography, and sleep diary. Bipolar Disord. 14, 870–879.
Livianos, L., Sierra, P., Arques, S., García, A., Rojo, L., 2012. Is melatonin an adjunctive stabilizer? Psychiatry Clin. Neurosci. 66, 82–83.
Maxwell, M., 1992. Family Interview For Genetic Studies. Clinical Neurogenetics Branch, Intramural Research Program NIMH.
McClung, C.A., 2013. How might circadian rhythms control mood? Let me count the ways…. Biol. Psychiatry 74, 242–249.
Millar, A., Espie, C.A., Scott, J., 2004. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. J. Affect. Disord. 80, 145–153.
Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry: J. Ment. Sci. 134, 382–389.
Morgenthaler, T., Alessi, C., Friedman, L., Owens, J., Kapur, V., Boehlecke, B., Brown, T., Chesson , A., Coleman, J., Lee-Chiong, T., Pancer, J., Swick, T.J., 2007. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 30, 519–529.

Mullin, B.C., Harvey, A.G., Hinshaw, S.P., 2011. A preliminary study of sleep in adolescents with bipolar disorder, ADHD, and non-patient controls. Bipolar Disord. 13, 425–432.
Netzer, N.C., Stoohs, R.A., Netzer, C.M., Clark, K., Strohl, K.P., 1999. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann. Intern. Med. 131, 485–491.
Nurnberger , J.I., Berrettini, W., Tamarkin, L., Hamovit, J., Norton, J., Gershon, E., 1988. Supersensitivity to melatonin suppression by light in young people at high risk for affective disorder. A preliminary report. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 1, 217–223.
Pacchierotti, C., Iapichino, S., Bossini, L., Pieraccini, F., Castrogiovanni, P., 2001. Melatonin in psychiatric disorders: a review on the melatonin involvement in psychiatry. Front. Neuroendocrinol. 22, 18–32.
Ritter, P.S., Marx, C., Lewtschenko, N., Pfeiffer, S., Leopold, K., Bauer, M., Pfennig, A., 2012. The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. J. Neural Transm. 119, 1173–1184.
Rocha, P.M.B., Neves, F.S., Corrêa, H., 2013. Significant sleep disturbances in euthymic bipolar patients. Compr. Psychiatry 54, 1003–1008.
Salvatore, P., Ghidini, S., Zita, G., De Panfilis, C., Lambertino, S., Maggini, C., Baldessarini, R.J., 2008. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. Bipolar Disord. 10, 256–265.
Scott, J., 2011. Clinical parameters of circadian rhythms in affective disorders. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 21 (4), S671–S675.
Soreca, I., Wallace, M.L., Frank, E., Hasler, B.P., Levenson, J.C., Kupfer, D.J., 2012. Sleep duration is associated with dyslipidemia in patients with bipolar disorder in clinical remission. J. Affect. Disord. 141, 484–487.
St-Amand, J., Provencher, M.D., Bélanger, L., Morin, C.M., 2012. Sleep disturbances in bipolar disorder during remission. J. Affect. Disord. 146, 112–119.
Tohen, M., Frank, E., Bowden, C.L., Colom, F., Ghaemi, S.N., Yatham, L.N., Malhi, G.S., Calabrese, J.R., Nolen, W.A., Vieta, E., Kapczinski, F., Goodwin, G.M., Suppes, T., Sachs, G.S., Chengappa, K.R., Grunze, H., Mitchell, P.B., Kanba, S., Berk, M., 2009. The International Society for Bipolar Disorders (ISBD) task force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 11, 453–473.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry: J. Ment. Sci. 133, 429–435.