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BIOLOGICAL PSYCHIATRY - ORIGINAL ARTICLE

The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls

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Abstract Sleep is highly altered during affective episodes in patients with bipolar disorder. There is accumulating evidence that sleep is also altered in euthymic states. A deficit in sleep regulation may be a vulnerability factor with aetiological relevance in the development of the disease. This study aims to explore the objective, subjective and lifetime sleep characteristics of patients with manifest bipolar disorder and persons with an elevated risk of developing the disease. Twenty-two patients with bipolar I and II disorder, nine persons with an elevated risk of developing the disorder and 28 healthy controls were evaluated with a structured interview to characterize subjective and lifetime sleeping habits. In addition, participants wore an actimeter for six nights. Patients with bipolar disorder had longer sleep latency and duration compared with healthy controls as determined by actigraphy. The subjective and lifetime sleep characteristics of bipolar patients differed significantly from healthy controls. The results of participants with an elevated risk of developing the disorder had subjective and lifetime characteristics that were largely analogous to those of patients with manifest bipolar disorder. In particular, both groups described recurring insomnia and hypersomnia, sensitivity to shifts in circadian rhythm, difficulties awakening and prolonged sleep latency. This study provides further evidence that sleep and circadian timing are profoundly altered in patients with bipolar disorder. It may also tentatively suggest that sleep may be altered prior to the first manic episode in subjects at high risk.

Keywords Bipolar disorder · Sleep · Circadian rhythm · Early recognition

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Introduction

Bipolar disorder is a severe recurrent psychiatric condition, with a detrimental effect on patients' quality of life and socioeconomic status (Sierra et al. 2005). A dysfunctional regulation of sleep has been postulated to be a vulnerability factor and there is considerable evidence that disturbed sleep in adolescence conveys a long-term risk for the development of the disorder (Ritter et al. 2011).

While mania and hypomania are typically accompanied by a reduced need for sleep, insomnia or less commonly hypersomnia are the hallmarks of depressive episodes. Moreover, interepisode sleep also appears to be disrupted despite patients experiencing euthymia. Accumulating evidence suggests that alterations in sleep are not only an epiphenomenon of the disease process, but that the two are deeply intertwined (Harvey et al. 2005; Murray and Harvey 2010).

Bipolar patients have been found to sleep less efficiently and hold more dysfunctional and anxious beliefs regarding their sleep when compared with healthy controls (Harvey et al. 2005). Studies using actimetry have found the sleep of remitted bipolar patients to be more variable in length (Millar et al. 2004), longer (Harvey et al. 2005) and characterized by less wake time (Mullin et al. 2011).

The studies investigating the sleep of patients with bipolar disorder with polysomnography have produced inconsistent results. The most common finding has been a

shortened REM latency and a higher REM density (Fossion et al. 1998; Hudson et al. 1992; Knowles et al. 1986; Sitaram et al. 1982; Thase et al. 1989).

The hormone melatonin, which is secreted by the pineal gland during darkness, has been found to have an altered secretion pattern in patients with bipolar disorder (Nurnberger et al. 2000). Patients with bipolar disorder also appear to have a greater suppression of melatonin when exposed to light (Hallam et al. 2009).

Several genetic polymorphisms of circadian genes have been found to be associated with bipolar disorder, although these findings have not always been replicated (Benedetti et al. 2004a, b; Mansour et al. 2005; Soria et al. 2010).

Both unipolar and bipolar disorder have been conceptualised as states of internal desynchronisation. A deficit in the homeostatic sleep drive has been proposed as the cause of affective symptoms in vulnerable individuals (Wirz-Justice 2006, 2009).

The cognitive neurosciences have documented a close relationship between emotion regulation and sleep. Sleep deprivation has been shown to preferentially impair the retention of positive and neutral, but not negative stimuli (Walker and van der Helm 2009). A multitude of studies have shown poor sleep to amplify negative and mitigate positive emotional experiences on the subsequent day (Dinges et al. 1997; Zohar et al. 2005). Neuroimaging findings have demonstrated a greater magnitude of amygdala activation following sleep deprivation (Yoo et al. 2007).

Several studies have validated at risk criteria for psychosis and there is tentative evidence that early intervention may delay illness onset (McGorry et al. 2002). The early recognition of bipolar disorder is still in its infancy. At-risk criteria have been defined and are currently being validated (Conus et al. 2010; Correll et al. 2007; Leopold et al. 2012; Olvet et al. 2010). The early recognition of bipolar disorder appears to be vital on the one hand and potentially beneficial on the other because patients still experience a substantial delay from first symptoms until definitive treatment of approximately 5–12 years (Baldessarini et al. 2003; Pfennig et al. 2011).

The evidence accumulated so far indicates that a deficit in sleep regulation is likely to be risk factor for bipolar disorder (Ritter et al. 2011). The presented study aims to characterize the sleep of patients with bipolar disorder and subjects at high risk of developing the disease by structured interview focusing on subjective and lifetime aspects of sleep and circadian timing as well as actigraphy. Prior to conducting this study we defined three main hypotheses:

1. Bipolar patients sleep as measured by actimetry will be more fragmented, more variable, longer and marked by more frequent and lengthier wake periods. We also hypothesised bipolar patients to have extended sleep latency.
2. In terms of subjective and lifetime sleeping habits we hypothesised bipolar subjects to have more frequent periods of hypersomnia and insomnia, have a subjectively poorer quality of sleep and be more responsive to the influence of light.
3. High-risk persons will display some but not all of the alterations in sleep and circadian timing exhibited by bipolar subjects.

The results are discussed in relation to previous studies which employed actimetry in bipolar disorder.

Participants, materials and methods

Inclusion/exclusion criteria

All participants had to be at least 16 years of age and be euthymic at the time of investigation. Euthymia was broadly defined as having a score of $\leq$15 on the Hamilton Depression Rating Scale (HAMD-17) (Hamilton 1960) and a score of $\leq$10 on the Young Mania Rating Scale (YMRS) (Young et al. 1978). Participants with comorbid substance abuse, psychotic disorders or organic brain disorders, posttraumatic stress disorder or borderline personality disorder were excluded. Other psychiatric disorders were only deemed to satisfy exclusion, if the disorder would severely interrupt the ability to comply with the study protocol. In addition all prospective participants with sleeping disorders or other medical conditions likely to have an effect on sleep (i.e. chronic pain, heart failure) were excluded.

Participants

Three groups of participants were recruited into the study: patients with bipolar I and II disorder, persons with an elevated risk of developing bipolar disorder (hereafter "high-risk persons") and healthy controls. All participants were assessed using the Structured Clinical Interview for DSM IV (SCID-I) for axis 1 disorders and SCID-II for axis 2 disorders.

Patients with bipolar disorder

Patients with bipolar disorder were recruited via the bipolar clinic at the university hospital and through advertisements in psychiatric outpatient departments. The diagnosis was confirmed using the Structured Clinical Interview for DSM IV (SCID) (First et al. 1997) and all available records. Sedating medications (benzodiazepines, zopiclone, zolpidem,

antihistamines or barbiturates) were permitted if they had been taken at a stable dose for at least 1 month.

High-risk persons

Persons at high risk of developing bipolar disorder were recruited from the early recognition centre of the psychiatric university hospital in Dresden. Persons were considered to be at high risk if they fulfilled one of the two following criteria:

- A first or second degree relative with bipolar disorder, unipolar depression or schizoaffective disorder and sub threshold mood symptoms (as defined by the *Bipolar Prodrome Symptom Scale Vs.2*; C. Correll unpublished)

  or

- A previous episode of major depression with sub threshold mania symptoms.

Healthy controls

Healthy controls were recruited by advertisements in supermarkets, unemployment agencies and on the university campus. Exclusion criteria were

- a history of any psychiatric disorder (except for adjustment disorder in full remission),
- first-degree relatives with a psychiatric disorder (excluding dementias and adjustment disorder) and
- the use of any type of psychotropic medication (exception: antihistamines for allergic disorders) in the previous 4 weeks.

Materials and methods

Structured interview: BIPS-Q

Abnormalities of sleep and circadian rhythm in patients with bipolar disorder were collected via a systematic literature search. In addition, specific features often described by patients in clinical practice were accrued. Three domains were identified in which bipolar subjects seemed to differ from healthy controls:

- Sleep quality in general (i.e. difficulties initiating sleep or difficulties waking up in the morning)
- Temporal stability (i.e. recurrent hyper- or insomnia, sensitivity to alterations in sleep times)
- Reactivity of mood and sleep (i.e. the impact of external influences on mood and sleep).

A set of 33 questions exploring circadian timing and sleep were assembled by consensus and compiled to form the Bipolar Sleep Questionnaire (BIPS-Q). Answers were arranged on a Likert-scale with possible answers indicating frequency or severity of a particular symptom.

The questions were administered in the format of a structured interview. The average time taken was approximately 25 min.

Actimetry

The circadian rhythm and sleep of participants was evaluated using the SomnoWatch plus® actimeter (Somnomedics®, Randersacker, Germany). The device is micro-electro-mechanical-system (MEMS) based and contains a light sensor and an event marker. Raw activity is determined via three accelerometers and expressed in mg ($1\ g = 9.83\ m/s^2$). The sampling frequency was set to 32 Hz and the sleep-wake evaluation algorithm optimised by comparing six nights of parallel actimetry and polysomnography data. The algorithm was optimised to detect wake periods within sleep.

Raw data were evaluated using the software Domino-Light® (Somnomedics®, Randersacker, Germany) which provides a graphic user interface and calculates the pertinent sleep parameters (and allows for direct SPSS® export). The calculated parameters were

Time in bed (TIB) = Time from lying down to sleep until getting up in the morning
Sleep latency = Beginning of TIB until sleep onset
Activity = Cumulative raw activity (expressed in mg)
Sleep duration = Total amount of time spent asleep
Wake time = Time spent awake after sleep onset (excluding sleep latency)
Sleep efficiency = Percentage time asleep during TIB
Wake periods $\geq$3 min = Periods of wakefulness $\geq$3 min after sleep onset
Wake period/hour = Average number of wake periods per hour

Participants were asked to wear the actimeter on their non-dominant wrist for 6 days and remove it only when in contact with water. The participants were required to press the event-marker button at the time of settling down to sleep "eyes closed" and on awaking in the morning "eyes open" (but not whilst anticipating a return to sleep). The time in-between these two events was defined as "Time in Bed" (TIB) which provided the basis for the calculation of all relevant parameters.

The raw data was evaluated in a blinded fashion. The events demarcating TIB were examined for plausibility by comparison with the raw data. Where, the marked event was not plausible (i.e. continuous activity and light following "eyes closed") markers were set according to raw

data and sleep diary. In total 659 markings were plausible and 49 (6.9 %) had to be adjusted.

Study protocol

Following informed consent, all eligible participants were screened using the SCID (First et al. 1997). Euthymia was confirmed by HAMD and YMRS. Data on age, gender, education and sociodemographic status were collected. Participants were classified into those with and those without a regular daily routine. Participants who were in regular work, studying or taking care of a family were classified as having a regular routine. For patients with bipolar disorder or at high risk the number and polarity of episodes, suicide attempts and current medication were recorded. Bipolar patients were asked whether they had received and responded to lithium in the past.

During the first study visit euthymia was re-confirmed and the BIPS-Q was administered. Participants were familiarised with the actimeter and required to wear the device for 6 days. Participants were asked in advance to choose weeks in which no major distortion of their regular rhythm was to be anticipated (i.e. holidays, childbirth, marriage, exams).

Whilst wearing the actimeter participants completed an online-sleep diary. The data was used to verify TIB-periods.

Statistical analysis

Analyses were separated into those we assumed to be highly relevant (primary outcomes) and those that were more explorative in nature (secondary outcomes).

Primary outcomes

BIPS-Q Disturbed sleep, non-restorative sleep, episodic short ($\geq$3 days and $\leq$1 month) hyper- and insomnias, use of sedatives and frequency of response to light

Actimetry Mean and variability of total night time activity (cumulative total movement), wake periods $\geq$3 min and sleep duration.

All further parameters (i.e. prolonged ($\geq$1 month) insomnia and hypersomnia, sensitivity to shifts in rhythm (difficulties maintaining a regular sleep wake rhythm after going to bed unusually early or late) and difficulties awakening in the morning) were treated as secondary outcomes.

The data were tested for normal distribution and homogeneity of variance. The three groups were compared by MANCOVA. The standard deviation of each variable across six nights of measurement was used a marker of variability. Actimetry measures were converted into time-dependent units where time was a significant determinant (i.e. total night time activity). No group differences were found for sex and "regular daily rhythm". Differences were found for age, and age was therefore adjusted for.

The level of significance was set to $p \leq 0.05$. Post hoc pairwise, bonferroni-corrected comparisons were calculated.

SPSS®-Statistics Version 17.0.1 was used for all calculations.

The study was approved by the ethics committee (Medical Faculty, University of Dresden).

Results

There were no relevant differences in sociodemographic composition of the three groups an exception being a difference in mean age. Tables 1, 2, and 3 give a synopsis of the sociodemographic characteristics of all participants and the clinical features of bipolar and high-risk individuals.

High-risk subjects had experienced symptoms for an average of 3.0 years. Only one subject was receiving medication (Bupropion). All patients with bipolar disorder were receiving medication the most common being lithium and quetiapine.

Primary outcome, BIPS-Q

The results are subsumed within the categories sleep-quality, temporal stability and affective reactivity.

Sleep quality

Both bipolar subjects and high-risk subjects had significantly more frequent and intense sleep disturbances

Table 1 Sociodemographic characteristics of all participants

	High-risk ($n = 9$)	Bipolar ($n = 22$)	Controls ($n = 28$)
Age in years, mean (SD)	25.4 (3.6)	32.7 (10.0)	28.3 (7.2)
Male (%)	77.8	59.1	57.1
No vocational training (%)	0	0	3.6
Secondary education (%)	11.1	31.8	17.8
High school (%)	11.1	4.5	3.6
Qualified for entrance to university in (%)	77.8	63.6	75.0
Irregular daily rhythm (%)	0	13.6	3.6
Regular daily rhythm (%)	100	86.4	96.4
Employed/student (%)	100	90.9	96.4
Pension (%)	0	4.5	0

Table 2 Diagnostic features of high-risk and bipolar subjects

	High-risk ($n = 9$)	Bipolar ($n = 22$)
Single episode of major depression or recurrent depression (%)	77.8	0
Social phobia (%)	11.1	0
Bipolar disorder type 1, last episode manic (%)	0	36.4
Bipolar disorder type 1, last episode depressive (%)	0	50
Bipolar disorder type 2 (%)	0	13.6
No disorder on axis 1 (%)	22.2	0
Obsessive–compulsive personality disorder (%)	0	9.1
Histrionic personality disorder (%)	11.1	0
Narcissistic personality disorder (%)	0	4.5
No disorder on axis 2 (%)	88.9	86.4

Table 3 Clinical and treatment features of patients with bipolar disorder

Clinical features of patients with bipolar disorder (n = 22)	
Duration of illness, mean in years	13.5
Duration since diagnosis, mean in years	5.7
Total number of depressive episodes (mean)	5.5
Total number of manic and hypomanic episodes (mean)	4.6
Lithium response	68.2 %; (13.7 % without lithium exposure)
Suicide attempt with high lethality	13.6 %
Suicide attempt with low lethality	31.8 %
Medication (in % and fraction of total)	
Lithium	63.6 % (14/22)
Valproic acid	36.4 % (8/22)
Quetiapine	40.9 % (9/22)
Lamotrigine	13.6 % (3/22)
Carbamazepine	9.1 % (2/22)
Olanzapine	4.5 % (1/22)
Clozapine	4.5 % (1/22)
Aripiprazol	4.5 % (1/22)
Antidepressants (Venlafaxine, Escitalopram, Citalopram and Mirtazapine each 1/22)	18.2 % (4/22)

compared with healthy controls. Similarly, both groups complained about significantly higher levels of unrestorative sleep (Table 4).

Table 4 BIPS-Q results sleep quality

BIPS-Q item	Group	Mean	F	df	p
Frequency of disturbed sleep	BIP	1.899	4.9	2	0.011
0 = never	HR	1.901			
6 = daily and continuously	CONTR	0.361			
Intensity of disturbed sleep	BIP	1.673	6.1	2	0.004
0 = none	HR	2.065			
6 = extreme	CONTR	0.272			
Frequency of not feeling rested in the morning	BIP	2.429	7.3	2	0.002
	HR	4.312			
0 = never	CONTR	1.455			
6 = daily and continuously					
Intensity of not feeling rested in the morning	BIP	1.418	12.6	2	<0.001
	HR	3.549			
0 = none	CONTR	0.745			
6 = extreme					
Use of sedatives or alcohol to aid sleep	BIP	1.448	4.2	2	0.020
	HR	0.173			
0 = never	CONTR	0.092			
6 = daily and continuously					

BIP bipolar group, *HR* high-risk group, *Contr* control group

Temporal stability

Both bipolar patients and high-risk persons expressed significantly more frequent short episodes (≥3 days, ≤1 month) of insomnia and hypersomnia (Fig. 1). Both groups also described episodes of increased need for sleep that were significantly more frequent and of greater magnitude. Bipolar patients and high-risk persons also stated to have more frequent episodes of reduced need for sleep, but only the magnitude of sleep reduction was significant.

Reactivity

Bipolar patients expressed a greater dependence of mood on light. This difference was not statistically significant.

Primary outcome, actimetry

Patients and high-risk persons generally had higher night time activity levels although these were statistically not significant, when adjusted for time (Fig. 2a). The variability of night time activity levels was significantly elevated, particularly in high-risk subjects. No differences were found regarding wake periods lasting longer than 3 min.

Bipolar subjects had significantly elevated sleep duration (Fig. 2b). A subsequent t test showed a significant influence of sedating medication (quetiapine, clozapine and olanzapine) on sleep duration (Table 5). It ought to be

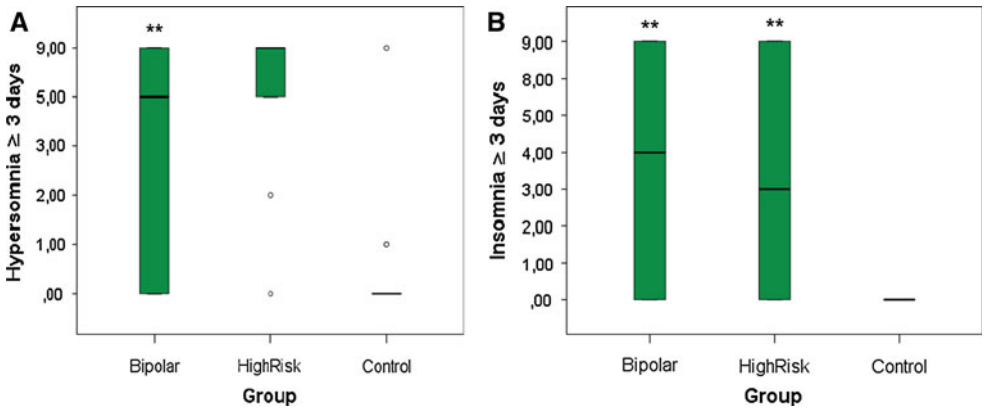

Fig. 1 *BIPS-Q results* Recurrent short hypersomnia (**a**) and recurrent short insomnia (**b**). The number of episodes is shown on the *y*-axis with 9 denoting >8 times. Post hoc pairwise comparison, $^{**}p < 0.01$ versus control

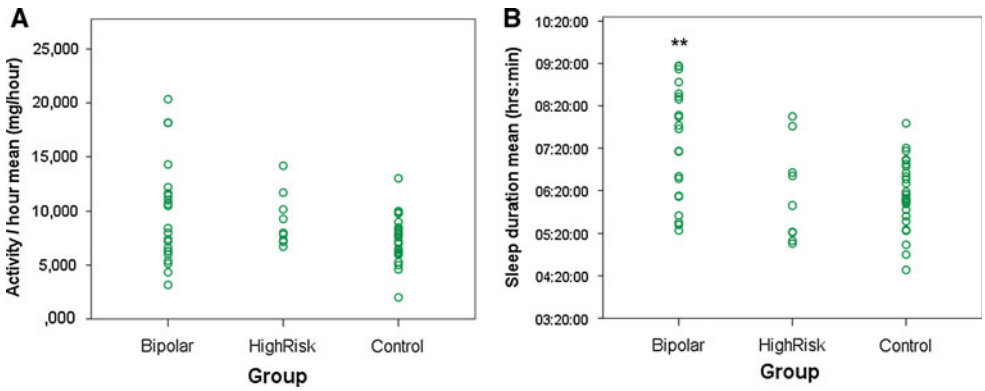

Fig. 2 *Actimetry* Activity per hour in mg (**a**) and Sleep duration (**b**). Post hoc pairwise comparison, $^{**}p < 0.01$ versus control

Table 5 Sleep duration in patients receiving and not receiving sedating atypical antipsychotics (*t* test)

Bipolar patients	*n*	Sleep duration hrs.min.sec (SD in min)	*p*
Sedating medication	11	8.07.54 (51.05)	0.020
No sedating medication	11	6.46.03 (24.08)	

SD standard deviation

noted though that the total mean sleep duration of bipolar patients without sedating medication still remained approximately 30 min longer than that of healthy controls.

Secondary outcomes, BIPS-Q

High-risk persons complained of significantly higher levels of sleep specific worries. In the post hoc analysis this result was significant when compared with either control or bipolar subjects. The subjective time required to fall asleep was elevated amongst bipolar and high-risk subjects. Both bipolar patients and high-risk persons described greater difficulties waking up in the morning and it took both groups longer than healthy controls to leave their bed after being woken. Bipolar patients had more frequent and longer naps during daytime.

Bipolar and high-risk subjects described difficulties maintaining a regular rhythm, when this had been disrupted by going to bed very late. Only high-risk subjects had difficulties maintaining their rhythm when they had gone to bed early.

While high-risk subjects recalled prolonged episodes of insomnia (≥1 month) significantly more frequently, bipolar patients had particularly high rates of recurrent prolonged hypersomnia (≥1 month).

Both patients with bipolar disorder and high-risk subjects described a stronger interdependence of mood and sleep (both sleep deprivation and extended sleep). The same was true for the intensity of the relationship between light and mood. Both bipolar patients and high-risk subjects used light actively to improve their mood.

No significant differences were found with regard to movement during sleep, phase shift at weekends, evening routine, restlessness or agitation before going to bed, difficulties compensating after changes from or into daylight savings time or with regard to disturbed sleep in advance of significant life events.

Secondary outcomes, actimetry

Patients with bipolar disorder spent significantly more time in bed (TIB) compared with high-risk persons and healthy

Table 6 Actimetry results, secondary outcomes

Group	Sleep latency (min.s)	Time in Bed (h.min)	Wake time after SO (min.s)	Sleep efficiency	Wake periods per hour
BIP	11.12	9.06	87.00	81.85	1.38
HR	8.18	7.30	69.24	83.20	1.56
CONTR	7.00	7.36	75.36	81.96	1.65
p	0.036	<0.001	0.359	0.886	0.091

HR high-risk, *BIP* bipolar, *CONTR* healthy control subjects, *SO* sleep onset, *h* hours, *min* minutes, *s* seconds

controls. Numerically bipolar patients had fewer wake periods, but this difference did not reach statistical significance.

Patients with bipolar disorder had significantly elevated sleep latency. High-risk subjects also needed longer to get to sleep, but this was not statistically significant compared with control subjects on post hoc testing.

No differences were found for wake after sleep onset, sleep efficiency and wake periods per hour. There was also no significant difference in the variability of the individual parameters. The results are summarized in Table 6.

Discussion

The results are compared with our initial hypothesis and then discussed in relation to the current literature on the topic.

Hypotheses

1. Hypothesis 1 was only partially confirmed by the results. Patients with bipolar disorder had significantly elevated sleep latency, sleep duration and time in bed. The sleep duration was influenced by medication, but differences could not be attributed to the sedating effect of medication alone. Wake time after sleep onset was non-significantly elevated in the bipolar group, but sleep fragmentation (activity/hour, wake periods/hour) appears to be equal or less in bipolar subjects. Across all parameters there was a small numerical increase in the variability of sleep parameters, but with the exception of activity per hour this did not reach statistical significance.
2. Hypothesis 2 was fully confirmed by the results of this study. The subjective and lifetime sleeping habits of bipolar patients deviated from the result obtained from healthy controls. Within 30 out of 39 domains bipolar subjects differed significantly. Both episodic short and prolonged hypersomnia as well as short and prolonged insomnia had occurred more frequently in patients with bipolar disorder.
3. With regard to the variables determined by actimetry, high-risk subjects were generally closer to the results obtained from healthy controls. Merely sleep latency and activity/hour were showed a similar divergence in bipolar and high-risk subjects. Amongst the items determined by BIPS-Q the results obtained from high-risk subjects closely mirrored those of bipolar patients in 27 out of 30 domains. In particular, high-risk persons also recalled recurring insomnia and hypersomnia significantly more frequently than healthy controls.

BIPS-Q

Similar to a study conducted by Harvey et al. (Harvey et al. 2005) bipolar patients experienced prolonged sleep latency and poorer quality of sleep. Both studies found a large discrepancy between the subjectively experienced and objectively measured sleep latency. Patients in this study estimated their sleep latency to be in the region of 16–30 min as opposed to 11 min as measured by actimetry. Harvey et al. found an even greater discrepancy of app. 30 min (Acti. 18.5 min; Subj. 49.1 min). Control subjects were more precise, but tended to underestimate their sleep latency in both studies. A similar tendency was replicated by Mullin et al. (2011) in adolescents with bipolar disorder. The subjective estimates of poor and fragmented sleep quality were at odds with the objective finding of more continuous sleep.

Hypersomnia is a frequent symptom in bipolar depression with estimated rates between 23 and 78 % (Casper et al. 1985; Detre et al. 1972). Patients described recurring hypersomnia, but it remains unclear whether this was only experienced during depression, interepisode or prior to the first episode. Interestingly post hoc analysis showed no correlation of prolonged hypersomnia with the number of prior depressive episodes, but moderate correlation with the number of prior manic episodes. There are no prospective studies available evaluating hypersomnia in healthy individuals as a risk factor for later mania. Two studies have, however, evaluated the clinical course of patients with hypersomnia and found this symptom to be a significant risk factor for the development of depression within 1–3.5 years (Breslau et al. 1996; Ford and Kamerow 1989).

Bipolar patients reported more frequently to be concerned, not to be able to sleep, but rates of psychomotor agitation or restlessness of thought were reported less frequently compared to the Harvey study (Harvey et al. 2005).

Patients described substantial difficulties in resuming their normal rhythm after going to bed late. An extreme expression of this tendency is found in patients with delayed sleep phase syndrome (DSPS). These results are matched by genetic studies, which have found bipolar subjects to carry polymorphisms associated with DSPS, but not those associated with advanced sleep phase syndrome (ASPS) (Ebisawa et al. 2001; Nievergelt et al. 2006; Pirovano et al. 2004; Toh et al. 2001).

Bipolar subjects used light more frequently to improve their mood and described a greater magnitude of improvement on exposure to light. This finding is in keeping with persistent changes to the photoneuroendokrine-system in bipolar patients as described by Hallam et al. (2005a, b). The authors also postulate that the mechanism of mood stabilizers may in part be explained by their effect on melatonin suppression by light. The precise mechanisms by which light and mood interact have so far not been elucidated.

Retrospective studies in patients with bipolar disorder suggest that sleep disturbances may be a risk factor (Hosteteter et al. 1997; Lish et al. 1994; Rucklidge 2008). High-risk subjects had elevated subjective sleep latency in our study. The retrospective study by Rucklidge et al. found 60 % of bipolar subjects to have had this symptom in adolescence as opposed to 28.6 % of healthy control subjects (not significant at $p \leq 0.01$). High-risk subjects also described short and prolonged insomnia more frequently than bipolar patients and had a higher incidence of recurrent brief hypersomnia in our study. High-risk subjects also described a recurrent reduced need for sleep of greater magnitude compared with bipolar subjects. In the aforementioned study by Rucklidge 3.6 % of control subjects and 32.0 % of bipolar patients purported to have had this symptom prior to their first episode (not significant at $p \leq 0.01$). Despite the paucity of evidence, the results of the high-risk subjects appear to be broadly in line with previous findings.

Actimetry

Four prior studies have evaluated the sleep of patients with bipolar disorder via actimetry. These studies were published between 2004 and 2011. It is important to bear in mind that a comparison of absolute results is limited by the differences in apparatus and evaluating software (Table 7).

In accordance with all four prior studies bipolar patients had elevated sleep duration. Only one study demonstrated a significantly raised variability amongst bipolar subjects. Sleep diary-based studies have also found longer sleep duration amongst patients with bipolar disorder. In a study by Bauer et al. approximately 51 % of patients with bipolar disorder slept more than 9 h per night (Bauer et al. 2009). There is currently no plausible hypothesis why bipolar subjects spend more time asleep, since this phenomenon cannot be explained by medication alone.

Sleep latency has also been uniformly found to be prolonged in bipolar subject. However, this finding was only statistically significant in our study. The variability has also generally been found to be higher. Taking into account the fact that a substantial number of patients will have been receiving sedating medication, the "true" sleep latency is presumably even higher. One hypothesis that has been put forward states that the prolonged sleep latency observed in bipolar disorder may be due to difficulties in the regulation

Table 7 Summary of actimetry studies in bipolar subjects

Study	*n*	Sleep-duration/ (variability)	Sleep latency/ (variability)	Sleep efficiency/ (variability)	Wake time/ (variability)	Fragmentation/ (variability)
Millar et al. (2004)	Bip = 19 Cont = 19	↑/(↑*)	↑/(↑)	↓/(↑)	↑[b]/(↑)*	nc
Harvey et al. (2005)	Bip = 20 Cont = 20	↑*/(nc)	↑/(nc)	nc/(nc)	↑[a]/(nc)	nc
Jones et al. (2005)	Bip = 19 Cont = 19	↑/(↑)	↑/(↑)	↓/(↓)	↑[b]/(↑)	→/(→)
Mullin et al. (2011)	Bip = 13 Cont = 21	↑*/(→)	↑/(↑)	↑/(nc)	↓*[a]/(nc)	nc
This study	Bip = 22 Cont = 28	↑*/(↑)	↑*/(↑)	→/(→)	↑[a]/(↑)	→/(→)

nc not calculated

↑ Elevated in bipolar subjects, ↓ elevated in control subjects, → identical in both groups

* $p \leq 0.05$

[a] Wake time after sleep onset

[b] Total wake time

of arousal in response to positive emotional stimuli (Talbot et al. 2009).

Results regarding sleep efficiency are inconsistent and no differences were found in this study. The same applies to wake time after sleep onset. Two studies (including this study) have found wake time after sleep onset to be elevated and one has found it to be significantly lowered. However, the study by Mullin et al. was conducted in adolescents and results may not be applicable to the population in our study. Only Jones et al. (2005) calculated sleep fragmentation. The results were inconclusive with regard to fragmentation. In this study three markers of fragmentation were used (activity per hour, wake periods per hour and wake periods $\geq$3 min), but the results were inconclusive.

To our knowledge, only one study evaluating the sleep of adolescents at high risk of bipolar disorder via actimetry has been published (Jones et al. 2006). Twenty-two adolescents aged 13–19 years who had at least one parent with bipolar disorder wore an actimeter for 7 days. The offspring of bipolar patients had longer sleep duration, but shorter sleep latency and less (Jones et al. 2006) fragmentation. Due to the difference in age (mean 16.2 years) and the inclusion of offspring with previous manic episodes or cyclothymia the results are of limited value for comparison. In our study only the night time activity was significantly elevated compared with control subjects, while the wake periods were fewer. No conclusions with regard to sleep fragmentation can therefore be drawn.

Limitations

The following limitations have to be taken into account when interpreting our results. The patients with bipolar disorder were largely recruited from a specialist clinic at a university hospital and may therefore not be representative for the population of bipolar patients at large. The same is true for high-risk persons, who sought help due to being symptomatic.

Bipolar subjects may have been subject to a certain amount of recall bias regarding their sleep habits, since bipolar subjects are generally aware of the importance of regular sleep in the prevention of mood episodes.

Half of all participating bipolar subjects received sedating antipsychotics. These subjects had significantly elevated sleep duration. The precise effect of medication is difficult to quantify although some authors have attempted to adjust for this aspect (Eidelman et al. 2010). Other mood stabilizers also have subtle effects on sleep and the effect of combining different substances is impossible to quantify. Post hoc correlation revealed a modest but significant association between recurrent insomnia and use of sedating atypical antipsychotics which could suggest that a greater difference in sleep quality is being masked by the use of sedating medication. However, confining sleep studies in bipolar disorder to patients who are not receiving treatment would likely distort results, since these patients are almost certainly phenotypically different from those receiving medication. Discontinuing medication in bipolar patients, on the other hand, would be dangerous and unethical.

As a method actimetry is inferior to polysomnography because sleep or wake states can only be inferred from movement. There have also been doubts about the utility of actimetry to detect arousals in patients with insomnia or manifest sleep disorders (Sadeh et al. 1995; Sivertsen et al. 2006). More recently, however, technical advances and more refined evaluation algorithms have provided reasonable correlations between PSG and actimetry (Annie and Charles 2003; Sanchez-Ortuno et al. 2010). To optimize data quality we calibrated our algorithm with six nights of PSG. Most subjects wore the actimeter for six nights which is longer than the recommended five nights (Sadeh 2011).

The criteria by which high-risk subjects are defined are currently under evaluation. A positive family history carries a well-defined risk of developing bipolar disorder (Lichtenstein et al. 2009). Various symptoms have been postulated to be precursors of the disorder (Berk et al. 2007; Correll et al. 2008; Duffy et al. 2007), but there are no standardized instruments by which this risk can be delineated with any acceptable degree of precision. Therefore, it is not known how many of the high-risk subjects will develop manic symptoms.

In addition, a majority of high-risk subjects had suffered from a previous depressive episode. Alterations in sleep and circadian timing in unipolar depression have been extensively described (Riemann et al. 2001) and the differences between control and high risk subjects may well be entirely due to these known differences. The on-going longitudinal component of this study aims to assess the rate of conversion and will hopefully help to define characteristics of those with a prior depressive episode that progress to bipolar disorder.

Conclusion

The present study demonstrates that patients with bipolar disorder differ significantly in their lifetime sleeping habits and their subjective sleep experience from healthy controls. Bipolar subjects slept longer and had longer sleep latency as determined by actimetry. With regard to lifetime sleeping habits and subjective sleep experience the results of high-risk subjects were largely analogous to those of patients with bipolar disorder.

If sleep is thought of as a process vital in maintaining affective homeostasis and bipolar disorder is conceptualized

as a particularly severe defect in affective homeostasis, a deficiency in sleep regulation (or the component of sleep that is essential for maintaining affective equilibrium) would appear to be a plausible risk factor for the development of the disorder. Our study provides tentative evidence that an instability of sleep regulation as marked by recurring insomnia and hypersomnia, sensitivity to shifts in circadian rhythm, difficulties awakening and prolonged sleep latency may act as a vulnerability factor prior to the manifestation of manic episodes.

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