Research Paper

Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders

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Background: The nature of sleep-wake abnormalities in individuals with mental disorders remains unclear. The present study aimed to examine the differences in objective ambulatory measures of the sleep-wake and activity cycles across young people with anxiety, mood or psychotic disorders. **Methods:** Participants underwent several days of actigraphy monitoring. We divided participants into 5 groups (control, anxiety disorder, unipolar depression, bipolar disorder, psychotic disorder) according to primary diagnosis. **Results:** We enrolled 342 participants aged 12–35 years in our study: 41 healthy controls, 56 with anxiety disorder, 135 with unipolar depression, 80 with bipolar disorder and 30 with psychotic disorders. Compared with the control group, sleep onset tended to occur later in the anxiety, depression and bipolar groups; sleep offset occurred later in all primary diagnosis groups; the sleep period was longer in the anxiety, bipolar and psychosis groups; total sleep time was longer in the psychosis group; and sleep efficiency was lower in the depression group, with a similar tendency for the anxiety and bipolar groups. Sleep parameters were significantly more variable in patient subgroups than in controls. Cosinor analysis revealed delayed circadian activity profiles in the anxiety and bipolar groups and abnormal circadian curve in the psychosis group. **Limitations:** Although statistical analyses controlled for age, the sample included individuals from preadolescence to adulthood. Most participants from the primary diagnosis subgroups were taking psychotropic medications, and a large proportion had other comorbid mental disorders. **Conclusion:** Our findings suggest that delayed and disorganized sleep offset times are common in young patients with various mental disorders. However, other sleep-wake cycle disturbances appear to be more prominent in broad diagnostic categories.

Introduction

Sleep-wake cycle disturbances are part of the symptomatology of several mental disorders and commonly exacerbate the clinical profiles of such disorders. For instance, sleep-wake disturbances have been associated with worse symptom severity, greater functional impairment, increased risk for relapse and poorer quality of life in people with anxiety, mood or psychotic disorders.[1–7] However, the diagnostic specificity of sleep-wake disturbances in the mental health context remains unclear, particularly at early stages of illness.

The potential validity of objective sleep-wake cycle measures as biomarkers may provide objective measures to support early screening and diagnoses, shed light on some of the underlying pathophysiological mechanisms involved in various disorders, and clarify the rationale for sleep- and circadian-based treatment pathways. This is especially relevant in the context of youth. During this period of life, the initial symptomatology across various diagnoses is often subsyndromal and there is a great need for early biomarkers and adapted interventions.[8,9] Furthermore, sleep disturbances observed in young adults often start during childhood or adolescence[10] and are associated with the onset and persistence of psychological distress.[11,12]

Various studies have described sleep-wake profiles in cohorts of individuals with anxiety, mood or psychotic disorders compared with healthy controls. In most of these studies, the samples combined individuals across a wide age range

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(e.g., 17–50 yr[13] or 18–79 yr [14]). Studies focusing on individuals with anxiety have highlighted sleep initiation and maintenance (i.e., fragmented or poorly consolidated sleep) difficulties.[15–17] Similarly, in both community-based and clinical samples, depression has been associated with prolonged sleep onset latency, poorer sleep consolidation, extended or delayed sleep duration and phase shifts of the sleep-wake cycle.[14,18–24] Compared with age-matched controls, young people with bipolar disorder have longer sleep onset latency and increased nighttime awakenings, and they report worse sleep quality and spending extended time asleep.[25,26] The literature on psychotic disorders is scarcer, but compared with healthy controls, patients with schizophrenia have been found to have longer sleep onset latency, extended sleep duration and time in bed, delayed sleep-wake profiles and higher intraindividual variability.[27,28]

While the overlap in these findings raises questions about the specificity of these profiles, few comparative studies have investigated sleep-wake disturbances across multiple diagnoses. Epidemiologic data suggest that subgroups of people reporting anxiety or depression symptoms have elevated rates of insomnia, but these rates are higher in those with depression than in those with anxiety.[3] Conversely, in a sample of nonmedicated young patients (age 7–17 yr, it was observed that those with anxiety disorders had a longer sleep onset and a higher number of awakenings than those with major depression.[16] Furthermore, we recently demonstrated that young patients with bipolar disorder spend longer time in bed and have more delayed sleep-wake patterns than those with unipolar depression.[29]

A seminal meta-analysis based on 177 polysomnographic studies found sleep initiation difficulties and reduced sleep efficiency and duration in patients with anxiety, affective disorders or schizophrenia compared with controls (mean age 39.1 ± 14.8 yr).[30] The magnitude of the sleep duration reduction was found to be higher in the affective disorders subgroup and the average sleep efficiency was lower in the schizophrenia than in the affective disorders subgroup. Nevertheless, they reported fewer differences among the subgroups of patients than between these clinical subgroups and controls, suggesting poor diagnostic specificity. Aside from the potential methodological, cross-cultural or chronological differences inherent to the meta-analytic approach, this study integrated individuals from a large age range (64-yr span) distributed unequally across diagnostic groups.[31] Furthermore, it was oblivious to intraindividual variability, an important aspect of the sleep-wake cycle that is more easily assessed using ambulatory devices, such as actigraphy.

A case study reported that the actigraphic sleep profile of a patient with schizophrenia was somewhat delayed and more irregular than that of a depressed patient.[32] Other actigraphy studies have observed lowered activity levels in patients with depression or schizophrenia compared with healthy controls, with more pronounced differences in those with schizophrenia and particularly those taking antipsychotic medication.[13,33–35] Bipolar disorder has also been associated with higher variability in activity patterns and a phase advanced peak of the activity–rest cycle.[34,35] However, no study has yet investigated multiday sleep-wake and activity profiles across more than 2 diagnostic groups.

The present study aimed to compare objective measures of the sleep-wake and activity cycles in real life settings in young people (age 12–35 yr) with primary anxiety, unipolar depression, bipolar or psychotic disorders compared with a sample of healthy controls. We hypothesized that sleep-wake patterns would be characterized by a pronounced delay in those with bipolar disorder, by elevated variability in those with psychotic disorders and by poor sleep consolidation across most clinical subgroups.

Methods

Participants

We recruited individuals aged 12–35 years for participation in this study. Healthy controls who reported no history of mental illness were recruited from the community, and help-seeking patients with emerging mental disorders were recruited from early intervention services for mental health problems in young people (headspace, Camperdown and Campbelltown, Sydney, Australia[36,37]). As described elsewhere,[37] patients entering these youth-focused mental health services were managed by trained health professionals. All participants were assessed by a senior clinician (psychiatrist, clinical psychologist or mental health nurse) and by a trained research psychologist using a structured interview based on DSM criteria. These clinicians determined primary and secondary diagnoses based on the relative severity, time of onset and possible interactions between underlying etiologies. For instance, if for a given patient anxiety symptoms were more prominent than depressive symptoms or if a longstanding history of anxiety appeared to contribute to the emergence of depression, a diagnosis of primary anxiety and secondary depression would be attributed. Patients were divided into 4 groups according to primary diagnosis: anxiety disorder (e.g., social anxiety disorder, generalized anxiety disorder and obsessive–compulsive disorder), unipolar depression, bipolar disorder and psychotic disorder (e.g., schizophrenia, first-episode psychosis and schizoaffective disorder). Most participants with substance dependence were excluded because this was an exclusion criterion for other related studies. All participants were referred by a mental health professional who previously evaluated their ability to give informed consent. Participants were provided with an information statement document explaining that participation in this research would be entirely voluntary and that their decision whether to take part or not (or to take part and then withdraw) in this study would not affect their treatment or relationship with professionals at the Brain & Mind Research Institute. Participants then met with someone from the research team who explained the study, answered any questions and further assessed their ability to provide informed consent. Any potential participant who was deemed to be unable to provide informed consent was excluded from the study. All participants gave written informed consent. Written consent was obtained from the parents or legal guardians of all participants who were younger than 16 years. The study protocol

was approved by the University of Sydney Human Research Ethics Committee.

Procedures

Actigraphy does not measure vigilance states based on cortical activity and therefore provides indirect estimations of sleep measures. Nevertheless, to simplify the terminology in the present manuscript, sleep parameters estimated from actigraphy are defined as "sleep" and "wake." Herein, sleep-wake measures were obtained from 4 to 22 days of sleep diary and actigraphy monitoring (Actiwatch-64/L/2, Philips Respironics). Measures collected with these different actigraphy models have previously been shown to be equivalent.[38] The number of days of actigraphy monitoring was significantly lower in the control group than in all other groups ($F_{4,339}$ = 16.3, $p < 0.001$; see Table 1 for means). Data from Actiwatch-L were collected over 1-minute epochs, and data from all other actimeter models were collected over 30-second epochs. Only the main (i.e., longer) sleep episode from each 24-hour period was included in the analysis. Sleep onset/offset were automatically defined with Actiware 5.0 software (Philips Respironics) and were subsequently inspected visually by trained technicians using sleep diaries. Sleep intervals were subsequently submitted to dual integration to define periods spent awake and asleep, using a wake threshold value of medium sensitivity (40.0 activity counts per epoch).

The following sleep parameters calculated from actigraphy data were averaged over the monitoring period: sleep onset/offset (time points when it was estimated that participants fell asleep and woke up, respectively; mean timing of the onset/offset of the sleep episode), sleep period (total length of the sleep episode; period between sleep onset and sleep offset), total sleep time (amount of time scored as "sleep" within the sleep episode), wake after sleep onset (WASO; amount of time scored as "wake" within the sleep episode), and sleep efficiency (percentage of time spent asleep during the sleep period). The standard deviations of these 6 parameters were used as indicators of intraindividual sleep-wake cycle variability across the days of actigraphy monitoring. Furthermore, each individual with a mean sleep onset of 1:30 am or later and those with a mean sleep offset of 10:00 am or later were identified as having delayed sleep onset and offset, respectively. These timings were defined by calculating approximately 2 standard deviations from the means reported in the 19- and 24-year-old sample of an epidemiologic study.[39]

Individual actigraphy data sets were fitted to an extended Cosinor model[40] using nonlinear least squares regression in Prism 4 (GraphPad software). This generated 4 activity circadian curve parameters: amplitude (difference between the mean value and peak of the fitted curve, herein estimating the range of the activity levels across the 24-hour period), acrophase (a phase marker indicating the time when the fitted curve reaches its peak [i.e., time of maximal activity levels across the 24-hour period]), α (index of the width of the curve peak and troughs, with higher values indicating wider troughs or "inactive" portions of the cycle) and β (index of the steepness of the rise and fall of the fitted curve).

Statistical analysis

Statistical analyses were conducted with SPSS software version 21 (SPSS Inc.) and Statistica software version 6.1 (StatSoft Inc.). One-way analyses of covariance (ANCOVA) controlling for age, sex and number of actigraphy monitoring days were used to compare actigraphic sleep parameters across the 5 groups. Multiple comparisons of means on significant main effects were done using Fisher least significant difference (LSD) tests with Bonferroni correction (adjusted significance level $p \leq 0.005$). Cosinor α and β and all variability parameters were not distributed normally, and the regression slopes for at least 1 covariate were found to be heterogeneous for WASO, sleep offset and sleep efficiency. These variables were thus submitted to rank ANCOVA rather than traditional ANCOVA.[41] We used χ^2 tests to compare the proportions of participants with delayed sleep phase in each group. We also conducted supplemental sets of analyses excluding participants with fewer than 7 days of actigraphy monitoring and controlling for participants taking sedatives, hypnotics or stimulant medications in the entire sample for which medication information was available.

Results

Three hundred forty-two individuals aged 12–35 years participated in this study. Of these, 41 were healthy controls who reported no history of mental illness and 301 were patients with emerging mental disorders (56 with anxiety disorder, 135 with unipolar depression, 80 with bipolar disorder and 30 with psychotic disorders; see Table 1 for demographic and clinical characteristics). Information on current medication at the time of assessment was available for 61.4% of patients. Of those, 76.2% were taking psychotropic medications and 10.3% were taking sedative-hypnotic/stimulant medications (Table 1). Controls were slightly, but significantly, older than patients in all clinical groups, with mean age differences ranging from 2 to 5 years ($F_{4,337}$ = 11.9, $p < 0.001$; all contrast $p < 0.020$). After controlling for age, sex and the number of actigraphy monitoring nights, we found significant group differences for all sleep parameters and for the acrophase, α and β of the activity circadian curve. Means, standard deviations and omnibus statistics are reported in Table 2. Contrasts are detailed in the sections that follow.

Differences in sleep timing parameters across primary diagnosis groups

On average, sleep onset time tended to occur later in the anxiety ($p = 0.020$), depression ($p = 0.006$) and bipolar ($p = 0.011$) groups than in the control group (Fig. 1A). Compared with that seen in the control group, the proportions of individuals with a delayed sleep onset was significantly higher in the depression group (corrected $\chi^2_1 = 5.6$, $p = 0.018$) and tended to be higher in the primary anxiety group (corrected $\chi^2_1 = 3.4$, $p = 0.06$). Sleep offset time occurred significantly later in all 4 primary diagnostic groups than in the control group (all contrast $p < 0.001$), with the primary bipolar and psychosis groups showing the latest times. Accordingly, all primary

Table 1: Sample characteristics of the control group and the primary anxiety, depression, bipolar and psychosis groups

Characteristic*	Control *n* = 41	Anxiety *n* = 56	Depression *n* = 135	Bipolar *n* = 80	Psychosis *n* = 30	Statistic	*p* value
Sex, % female	53.7	48.2	65.2	75.0	33.3	$\chi^2_{(4)} = 21.8$	< 0.001
Age, yr; mean ± SD	25.3 ± 5.8	20.4 ± 5.1	20.0 ± 4.4	23.1 ± 5.3	22.5 ± 5.1	$F_{(4,337)} = 12.0$	< 0.001
Number of nights, mean ± SD	8.9 ± 3.1	11.9 ± 3.5	12.9 ± 3.1	12.4 ± 2.8	13.0 ± 1.8	$F_{(4,337)} = 16.3$	< 0.001
Occupational status, %							
Not working or studying	0	27.3	15.1	29.0	35.7	$\chi^2_{(4)} = 11.5$	0.022
Part-time	18.2	22.7	14.2	24.2	21.4	$\chi^2_{(4)} = 3.2$	0.52
Full-time	81.8	50.0	70.8	46.8	42.9	$\chi^2_{(4)} = 16.7$	0.002
Medication, %							
Currently medicated	0	51.4	73.6	80.0	75.0	$\chi^2_{(4)} = 90.0$	< 0.001
Taking antidepressants	0	37.8	60.4	34.0	35.0	$\chi^2_{(4)} = 46.8$	< 0.001
Taking mood stabilizers	0	8.1	18.7	56.0	15.0	$\chi^2_{(4)} = 51.2$	< 0.001
Taking antipsychotics	0	10.8	20.9	38.0	70.0	$\chi^2_{(4)} = 52.6$	< 0.001
Taking sedatives/benzodiazepines	0	2.7	5.5	8.0	5.0	$\chi^2_{(4)} = 3.8$	0.44
Taking stimulants	0	5.4	4.4	4.0	0	$\chi^2_{(4)} = 3.1$	0.54
Comorbidities, %							
Any comorbidity	0	10.7	41.5	27.5	43.3	$\chi^2_{(4)} = 39.6$	< 0.001
Anxiety	0	—	35.6	22.5	16.7	—	—
Depression	0	7.1	—	0	23.3	—	—
Bipolar disorder	0	0	0	—	3.3	—	—
Psychosis	0	0	0.7	0	—	—	—
Substance dependance	0	0	1.5	2.5	3.3	—	—
Eating disorder	0	0	4.4	1.3	0	—	—
Neurodevelopmental disorder	0	3.6	5.2	5.0	0	—	—
Somatoform disorder	0	0	1.5	0	0	—	—
Dissociative identity disorder	0	0	0	1.3	0	—	—

SD = standard deviation.
*Percentage of female participants in the total sample, means ± SD of age and number of actigraphy monitoring days and percentages of individuals in each occupational status categories (data available for 251 participants; 73.3% of the sample), taking medication (data available in 185 patients, 61.4% of the patient sample), and having comorbidities (data available for all patients).

Table 2: Sleep and circadian parameters derived from actigraphy for the control and primary anxiety, depression, bipolar and psychosis groups*

Parameter	Control *n* = 41	Anxiety *n* = 56	Depression *n* = 135	Bipolar *n* = 80	Psychosis *n* = 30	Statistic	*p* value
Average sleep parameters							
Sleep onset	23:18 ± 1:15	24:09 ± 1:35	24:05 ± 1:33	23:55 ± 1:25	23:51 ± 1:36	$F_{4, 334} = 2.5$	0.043
Sleep offset	7:39 ± 1:01	9:09 ± 1:38	8:52 ± 1:34	9:00 ± 1:33	9:17 ± 1:25	$F_{4, 337} = 7.2$	< 0.001
Sleep period, min	500.6 ± 60.1	539.7 ± 64.4	526.6 ± 62.1	545.1 ± 68.1	565.1 ± 89.5	$F_{4, 334} = 6.0$	< 0.001
TST, min	441.4 ± 53.0	459.7 ± 63.8	448.7 ± 53.8	472.3 ± 64.4	487.8 ± 94.1	$F_{4, 334} = 4.6$	0.001
WASO, min	59.2 ± 25.4	80.0 ± 32.8	77.1 ± 28.1	72.8 ± 24.7	76.1 ± 35.8	$F_{4, 337} = 4.4$	0.002
SE (%)	88.4 ± 4.3	85.2 ± 6.1	85.4 ± 4.8	86.6 ± 4.3	86.0 ± 6.9	$F_{4, 337} = 3.7$	0.006
Variability indexes							
Sleep onset SD	1:05 ± 0:36	1:24 ± 0:48	1:19 ± 0:48	1:26 ± 0:55	1:48 ± 1:01	$F_{4, 337} = 3.4$	0.010
Sleep offset SD	1:00 ± 0:24	1:27 ± 0:43	1:31 ± 0:50	1:31 ± 0:51	1:41 ± 0:45	$F_{4, 337} = 4.3$	0.002
Sleep period SD	76.6 ± 37.1	102.2 ± 38.9	96.6 ± 45.0	102.9 ± 54.4	113.0 ± 59.6	$F_{4, 337} = 3.2$	0.015
TST SD	65.8 ± 29.2	88.3 ± 35.5	83.7 ± 35.7	89.3 ± 50.0	99.2 ± 50.3	$F_{4, 337} = 3.1$	0.015
WASO SD	20.4 ± 11.8	26.9 ± 12.5	27.1 ± 15.2	24.8 ± 12.4	28.7 ± 18.9	$F_{4, 337} = 2.5$	0.046
SE SD	3.2 ± 1.6	3.8 ± 2.0	4.1 ± 2.1	3.6 ± 1.8	3.7 ± 2.1	$F_{4, 337} = 2.6$	0.037
Circadian activity rhythm							
Amplitude	1.72 ± 0.35	1.85 ± 0.53	1.92 ± 0.73	1.77 ± 0.51	1.77 ± 0.58	$F_{4, 297} = 1.3$	0.26
Acrophase	14:18 ± 3:31	16:23 ± 1:26	15:46 ± 4:22	16:05 ± 2:52	15:49 ± 1:27	$F_{4, 297} = 2.6$	0.038
α	–0.39 ± 0.24	–0.32 ± 0.21	–0.40 ± 0.28	–0.33 ± 0.27	–0.24 ± 0.27	$F_{4, 300} = 3.6$	0.007
β	10.19 ± 8.28	6.11 ± 3.95	7.34 ± 10.81	7.98 ± 7.09	6.09 ± 6.44	$F_{4, 300} = 3.3$	0.011

SD = standard deviation; SE = sleep efficiency; TST = total sleep time; WASO = wake after sleep onset.
*Means ± SD of actigraphic sleep and circadian parameters across primary diagnosis groups and statistics (analysis of covariance [sleep onset/offset, WASO, TST, SE] or rank analysis of covariance [α, β and all variability indexes: SD]). Contrasts results are reported in the text.

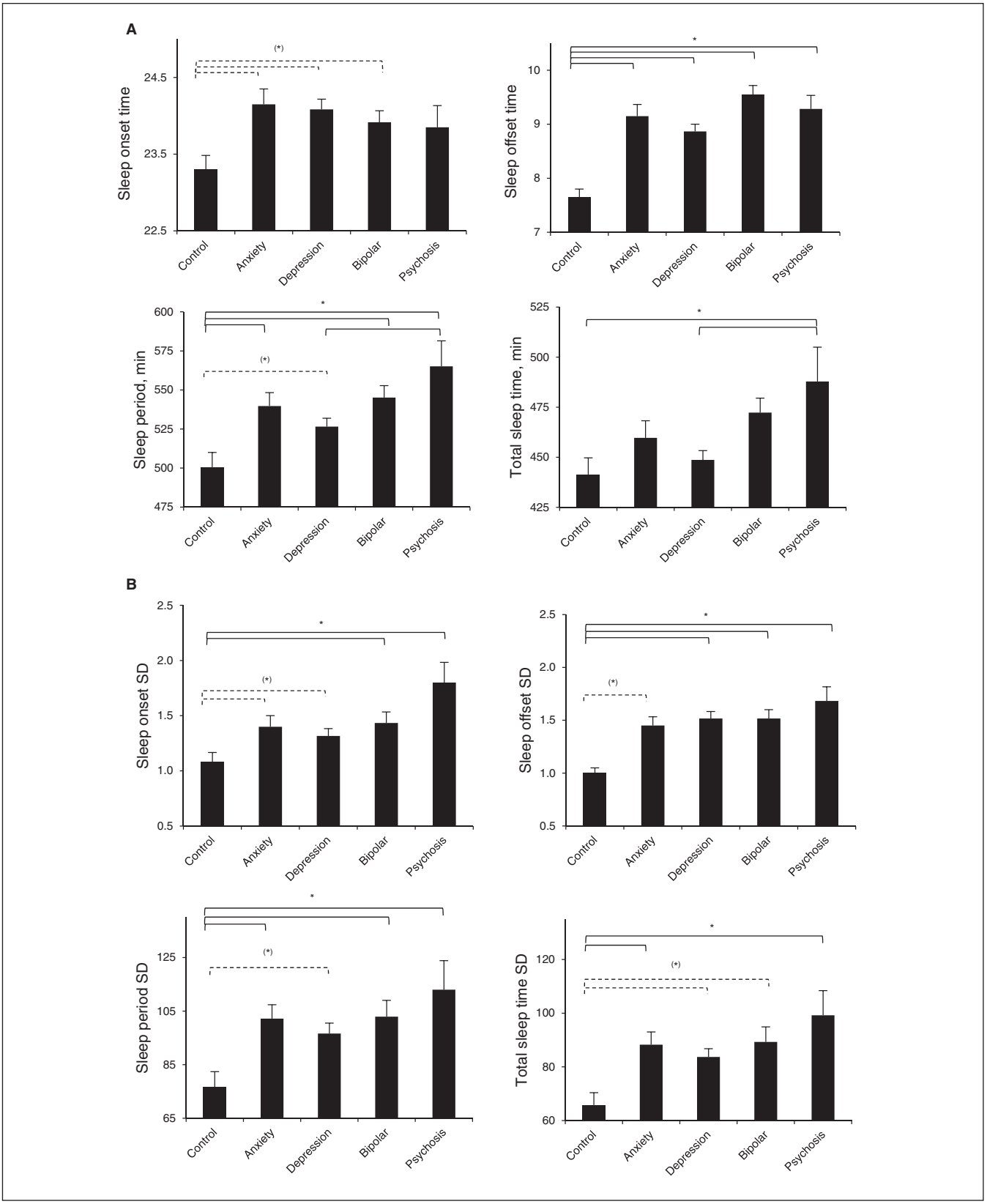

Fig. 1: Sleep timing parameters. The top panels **(A)** show average sleep timing parameters. The lower panels **(B)** show variability in sleep timing parameters across the monitoring period. Error bars indicate standard errors of the mean. Full lines indicate significant differences (*$p <$ 0.005) and dashed lines indicate trends ((*) $p \leq 0.020$). SD = standard deviation.

diagnostic groups had significantly higher proportions of individuals with delayed sleep offset times than the control group (all corrected $\chi^2_1 > 11.3$, $p \leq 0.001$). There was no significant difference in sleep onset and offset times among the 4 primary diagnostic groups.

The average sleep period was significantly longer in the anxiety ($p = 0.001$), bipolar ($p = 0.004$) and psychosis ($p < 0.001$) groups than in the control group (Fig. 1A). A similar trend was found for the depression group ($p = 0.019$). The psychosis group had a significantly longer sleep period than the depression group ($p = 0.001$). Total sleep time was significantly longer in the psychosis group than the control ($p = 0.001$) and the depression ($p < 0.001$) groups.

The variability in sleep onset time was significantly higher in the bipolar ($p = 0.004$) and psychosis ($p = 0.001$) groups than the control group (Fig. 1B). A similar trend was found for the anxiety ($p = 0.012$) and depression ($p = 0.013$) groups. The depression, bipolar and psychosis groups had significantly more variable sleep offset times than the control group (all $p < 0.001$). A similar trend was found for the anxiety group ($p = 0.005$). The anxiety ($p = 0.002$), bipolar ($p = 0.004$) and psychosis ($p = 0.005$) groups had significantly higher variability in sleep period than controls, with similar trends for the depression group ($p = 0.010$). The variability in total sleep time was significantly higher in the anxiety and psychosis groups than in the control group (both $p \leq 0.003$). A similar trend was found for the depression and bipolar groups (both $p = 0.007$). Overall, the psychosis and bipolar groups had the most variable sleep timing, but no significant difference in any sleep timing variability parameters emerged among the primary diagnostic groups.

Differences in sleep consolidation parameters across primary diagnosis groups

The anxiety, depression and bipolar groups had significantly more WASO than the control group (all $p \leq 0.001$; Fig. 2A). A similar trend was found for the psychosis group ($p = 0.018$). This was especially pronounced in the anxiety and depression groups ($p < 0.001$). Sleep efficiency was significantly lower in the depression than the control group ($p < 0.001$), with a similar trend for the anxiety ($p = 0.011$) and bipolar ($p = 0.008$) groups. There was no significant difference among the 4 primary diagnostic groups.

The variability in WASO was higher in the depression group than the control group ($p = 0.004$), and a similar trend was found for the anxiety group ($p = 0.006$; Fig. 2B). The variability in sleep efficiency was significantly higher in the depression than the control group ($p = 0.002$; Fig. 2B). No difference among the primary diagnostic groups reached the significance threshold for any of the sleep consolidation variability parameters.

Differences in activity circadian curve parameters across primary diagnosis groups

The anxiety ($p = 0.003$) and bipolar ($p < 0.005$) groups had a significantly later acrophase than the control group. A similar trend was found for the depression group ($p = 0.014$). The α was significantly larger in the psychosis group than the control and depression groups (both $p = 0.003$). The psychosis ($p = 0.001$) and anxiety ($p = 0.004$) groups had significantly lower β than the control group, and there was a similar trend for the depression group ($p = 0.007$). No significant group difference was found for the amplitude of the activity–rest cycle.

Discussion

To our knowledge, this is the first large scale study comparing objective sleep-wake measures and the circadian rhythm of the activity-rest cycle in real-life settings in a group of young people with various mental disorders. Our findings suggest that delayed and disorganized sleep offset times are common across mental disorders during youth. However, 2 main profiles of sleep-wake disturbances were observed: the subgroups with primary anxiety, depression and bipolar disorder were predominantly affected by marked sleep initiation difficulties and poor/unstable sleep consolidation, whereas the subgroup with primary psychotic disorder and, to a lesser extent, the subgroup with bipolar disorder were mostly characterized by prolonged sleep duration and showed the most unstable sleep schedules. Circadian activity profiles were found to be delayed in the groups with primary anxiety and bipolar disorder and to be somewhat misshaped in the group with primary psychotic disorder. It is important to note that these profiles cannot be solely attributed to primary diagnosis since they are also influenced by the effects of comorbities and psychotropic medication.

In line with the meta-analysis conducted by Benca and colleagues,[30] the current results suggest that some abnormalities of the sleep-wake cycle are common across primary diagnostic categories. Beyond the normal age-related changes occurring during youth, many of our young patients with mental disorders had a delayed sleep-wake profile. All primary diagnostic subgroups also presented with unstable sleep offset times, sleep period and total sleep time (although not reaching the corrected significance threshold for some subgroups). In individuals with affective and psychotic disorders, delayed and unstable sleep-wake profiles have been associated with abnormal endogenous melatonin rhythms.[27,42,43] Neurotransmitter dysfunctions associated with both circadian and psychopathological abnormalities, such as those found in the glutamate and dopamine systems,[44–48] represent other possible underlying mechanisms likely to influence these nonspecific sleep-wake abnormalities across primary diagnostic categories.

The profile observed in the subgroups with primary anxiety or mood disorders was characterized by disrupted and unstable sleep consolidation across multiple days, as well as a pronounced delay in sleep onset, a finding consistent with the sleep initiation difficulties reported in previous studies.[15–17] In the primary anxiety and bipolar groups, this was accompanied by a delayed activity peak in the afternoon. The primary anxiety group also presented a lower β suggestive of a slower fall and rise of activity levels in the evening and morning. The clinical profile of depressed and anxious individuals is perhaps most attuned with nighttime ruminations and sleep-related performance anxiety. In the context of both anxiety and affective

disorders, difficulties in sleep initiation and maintenance have been postulated to result from hyperarousal and/or impaired sleep drive.[49–52] This is likely to feed a vicious cycle between sleep disturbances and mood alterations. For instance, elevated cortisol around sleep onset has been associated with depression recurrence in adolescents.[53]

Prolonged sleep duration and sleep period in the context of unstable sleep onset times and overall marked sleep schedule variability seemed to be more characteristic of the subgroups with primary psychotic and, to a lesser extent, bipolar disorders. This is in line with overlaps in the genetic factors and symptomatology linked to bipolar and psychotic disorders, especially in those with early onset of illness.[54–56] Of note, some of these common genetic markers are also involved in circadian regulation.[57] From this perspective, the current findings of similar sleep timing phenotypes across primary bipolar and psychotic disorders reinforce the hypothesis of common circadian deregulation mechanisms in these pathologies. The potential influence of medications also needs to be considered since antipsychotics, known for their sedative effects, are commonly used in the treatment of both bipolar and psychotic disorders. In addition to longer sleep durations, the psychotic group was characterized by a wider "inactive" portion of the activity cycle (larger α). Interestingly, this group was also characterized by a slower rate of changes across the 24-hour period (smaller β). These abnormalities in the shape of the circadian rhythm of activity may reflect some degree of disorganisation in the biological clock.

Sleep-wake and circadian disturbances can have pervasive consequences on physiologic, occupational, social, cognitive and affective aspects of life. Many of these consequences are likely to interact with the pre-existing challenges inherent to mental disorders and to alter the ability to cope with these challenges.[6,58–60] Notably, daily changes in sleep timing and sleep efficiency have been found to covary with changes in psychotic and affective symptom severity in patients with schizophrenia.[61] These disturbances tend to appear early in the course of mental disorders, and it is reasonable to expect that their early treatment is likely to improve prognosis and, in some cases, possibly prevent the development of full-blown disorders. For example, longitudinal and interventional studies indicate that the normalization of sleep-wake disturbances is associated with lower rates of future illness onset.[3,62]

Therapeutic interventions aiming to stabilize sleep-wake schedules at earlier age-appropriate times may be relevant in youth in several mental disorder subgroups. These may include circadian-based interventions, such as melatoninergic

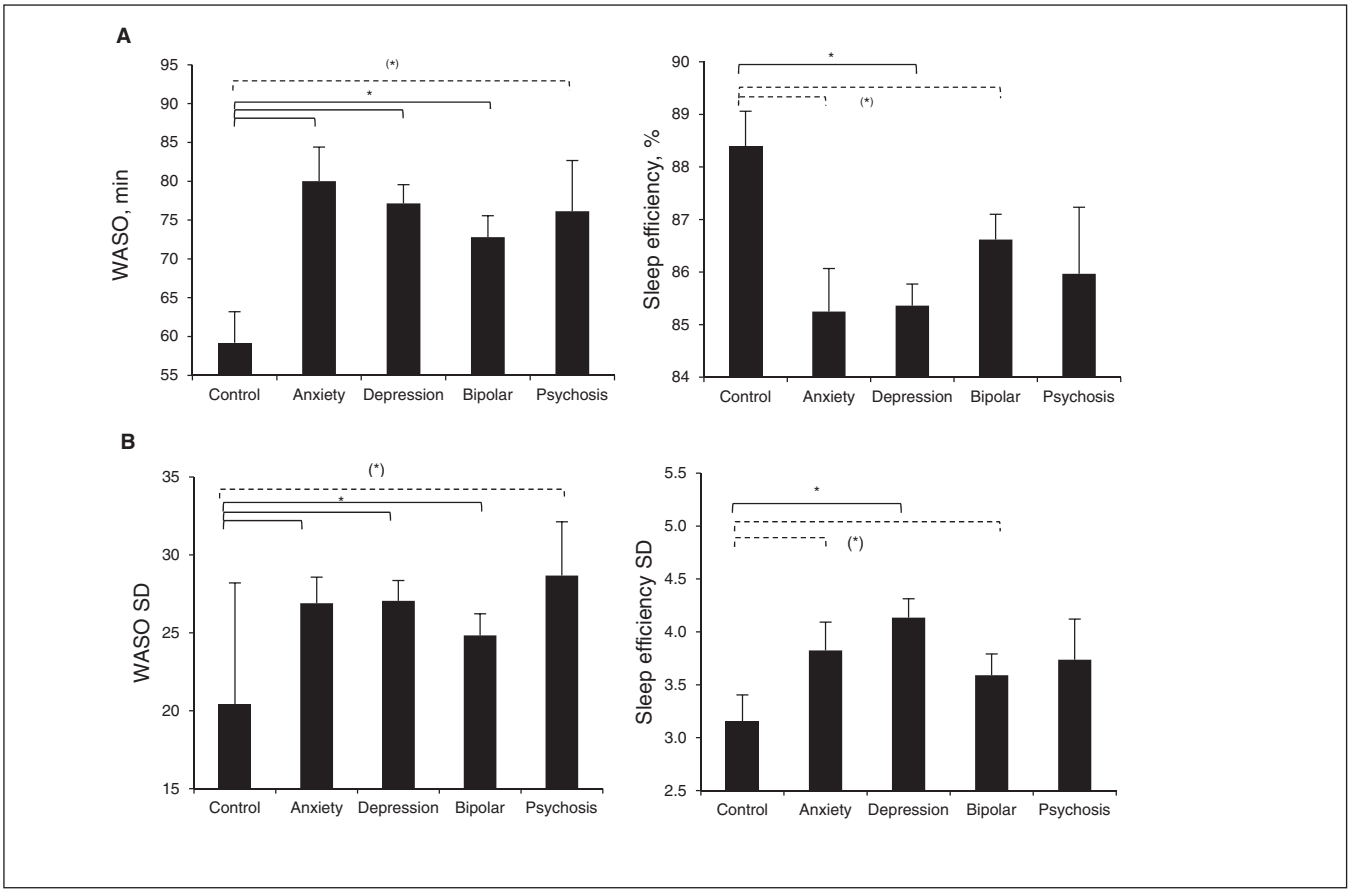

Fig. 2: Sleep consolidation parameters. The top panels **(A)** show average sleep consolidation parameters. The lower panels **(B)** show variability in sleep consolidation parameters across the monitoring period. Error bars indicate standard errors of the mean. Full lines indicate significant differences (*$p < 0.005$) and dashed lines indicate trends ((*) $p \leq 0.020$). SD = standard deviation; WASO = wake after sleep onset.

agents or light exposure manipulations.[63,64] Furthermore, young people with more prominent anxiety or affective disturbances may also benefit from relaxation techniques and cognitive-behavioural strategies targeting difficulties in sleep initiation and maintenance. Also, stabilizing the biological clock and establishing and maintaining appropriate sleep duration, notably by enforcing regular and earlier prebedtime routine and wake-up times, may be especially relevant for those with primary bipolar or psychotic disorders.

Limitations

Our participant sample extended from preadolescence to adulthood, periods known to differ both in terms of psychiatric symptoms, sleep and circadian rhythms. However, we attempted to control for this limitation in our statistical approach. The length of the actigraphy monitoring period varied from 4 to 22 days, but similar results were found in the subset of participants with at least 7 days of data (see the Appendix, Table S1, available at jpn.ca; we note that some results became trends or nonsignificant, which could notably be influenced by lower statistical power). Furthermore, information about current occupational status and medication at the time of assessment was not available for some of the participants. Herein, it is not possible to differentiate the contribution of primary diagnostic subgroups from that of altered occupational life or the effects of various medications on the observed sleep-wake profiles. Nevertheless, the aim of this study was to determine the sleep-wake profile of young persons with various mental disorders in real-life settings. Medication is part of the reality of most persons living with mental disorders and, from this perspective, their potential effects on the sleep-wake cycle is part of their real-life profile. Detailed analysis of the impacts of medication on sleep is beyond the scope of the present study, but results from the additional analyses presented in the supplemental material suggest that most group differences remained significant when controlling for the use of sedative-hypnotic/stimulant medication (with the exception of differences in the circadian acrophase, which became nonsignificant). Participants were categorized in each diagnostic group according to primary diagnosis, not taking into account comorbidities. For instance the considerable overlap between anxiety and depressive disorders could contribute to the sleep-wake profile similarities observed between these 2 subgroups. Future studies in which sample sizes would allow for balanced comorbidity subgroups should investigate the influence of comorbidities on sleep-wake profiles, notably comparing individuals with anxious-depressive syndromes to those with more isolated anxiety or depression. Furthermore, the time association between the emergence of sleep-wake disturbances and the onset and subsequent clinical course of mental disorders should also be assessed. For instance, it appears to be more common for insomnia to start before illness onset (or relapse) in the context of depression and after illness onset in the context of anxiety.[10,65] Also, we have previously found that the common delayed sleep-wake profile associated with mental disorders is worse in individuals at later clinical stages than in those at the early stages of illness.[66]

Conclusion

Based on multiple days of ambulatory sleep-wake monitoring in a cohort of young, mostly medicated patients with various mental disorders, the present findings reinforce the notion that sleep-wake disturbances are a hallmark of mental disorders. Young people with a primary diagnosis of anxiety, depression, bipolar disorder or psychotic disorders were found to be similarly affected by delayed and disorganized sleep patterns. Participants with primary anxiety or mood disorders showed marked sleep initiation difficulties with poor and unstable sleep consolidation, while those with primary psychotic and, to some degree, bipolar disorders were more prone to extended sleep duration seemingly linked to unstable sleep onset and oversleeping in the morning. Further studies are required to disentangle the effects of primary mental disorders from the effects of comorbidities and medications. Nevertheless, our findings underscore the importance of developing adapted sleep- and circadian-based interventions for young individuals with mental disorders.

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References

1. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;39:411-8.
2. Rohde P, Lewinsohn PM, Seeley JR. Comorbidity of unipolar depression: II. Comorbidity with other mental disorders in adolescents and adults. *J Abnorm Psychol* 1991;100:214-22.
3. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* 1989;262:1479-84.
4. Robillard R, Lambert T, Whitwell BG, et al. Sleep-wake patterns and mood disturbances in patients with psychotic disorders: a controlled study. *Sleep Med* 2011;12(Suppl 1):S53.
5. Perlis ML, Giles DE, Buysse DJ, et al. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *J Affect Disord* 1997;42:209-12.
6. Hofstetter JR, Lysaker PH, Mayeda AR. Quality of sleep in patients with schizophrenia is associated with quality of life and coping. *BMC Psychiatry* 2005;5:13.
7. Weissman MM, Greenwald S, Nino-Murcia G, et al. The morbidity of insomnia uncomplicated by psychiatric disorders. *Gen Hosp Psychiatry* 1997;19:245-50.
8. Hickie IB, Scott EM, Hermens DF, et al. Applying clinical staging to young people who present for mental health care. *Early Interv Psychiatry* 2013;7:31-43.
9. McGorry PD, Purcell R, Hickie IB, et al. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust* 2007;187(Suppl):S40-2.
10. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res* 2003;37:9-15.
11. Glozier N, Martiniuk A, Patton G, et al. Short sleep duration in prevalent and persistent psychological distress in young adults: the DRIVE study. *Sleep* 2010;33:1139-45.
12. Roberts RE, Roberts CR, Chen IG. Impact of insomnia on future functioning of adolescents. *J Psychosom Res* 2002;53:561-9.
13. Apiquian R, Fresán A, Muñoz-Delgado J, et al. Variations of rest-activity rhythm and sleep-wake in schizophrenic patients versus healthy subjects: an actigraphic comparative study. *Biol Rhythm Res* 2008;39:69-78.
14. Mendlowicz MV, Jean-Louis G, von Gizycki H, et al. Actigraphic predictors of depressed mood in a cohort of non-psychiatric adults. *Aust N Z J Psychiatry* 1999;33:553-8.
15. Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. *Sleep Med Rev* 2000;4:263-76.
16. Forbes EE, Bertocci MA, Gregory AM, et al. Objective sleep in pediatric anxiety disorders and major depressive disorder. *J Am Acad Child Adolesc Psychiatry* 2008;47:148-55.
17. Fuller KH, Waters WF, Binks PG, et al. Generalized anxiety and sleep architecture: a polysomnographic investigation. *Sleep* 1997;20:370-6.
18. Wehr TA, Wirz-Justice A, Goodwin FK, et al. Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science* 1979;206:710-3.
19. Ohayon MM, Caulet M, Lemoine P. Comorbidity of mental and insomnia disorders in the general population. *Compr Psychiatry* 1998;39:185-97.
20. Hasler BP, Buysse DJ, Kupfer DJ, et al. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. *Psychiatry Res* 2010;178:205-7.
21. Kitamura S, Hida A, Watanabe M, et al. Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. *Chronobiol Int* 2010;27:1797-812.
22. Tsujimoto T, Yamada N, Shimoda K, et al. Circadian rhythms in depression. Part II: circadian rhythms in inpatients with various mental disorders. *J Affect Disord* 1990;18:199-210.
23. Liu X, Buysse DJ, Gentzler AL, et al. Insomnia and hypersomnia associated with depressive phenomenology and comorbidity in childhood depression. *Sleep* 2007;30:83-90.
24. Hawkins DR, Taub JM, Van de Castle RL. Extended sleep (hypersomnia) in young depressed patients. *Am J Psychiatry* 1985;142:905-10.
25. Mullin BC, Harvey AG, Hinshaw SP. A preliminary study of sleep in adolescents with bipolar disorder, ADHD, and non-patient controls. *Bipolar Disord* 2011;13:425-32.
26. Roybal DJ, Chang KD, Chen MC, et al. Characterization and factors associated with sleep quality in adolescents with bipolar I disorder. *Child Psychiatry Hum Dev* 2011;42:724-40.
27. Wulff K, Dijk DJ, Middleton B, et al. Sleep and circadian rhythm disruption in schizophrenia. *Br J Psychiatry* 2012;200:308-16.
28. Martin J, Jeste DV, Caliguiri MP, et al. Actigraphic estimates of circadian rhythms and sleep/wake in older schizophrenia patients. *Schizophr Res* 2001;47:77-86.
29. Robillard R, Naismith SL, Rogers NL, et al. Delayed sleep phase in young people with unipolar or bipolar affective disorders. *J Affect Disord* 2013;145:260-3.
30. Benca RM, Obermeyer WH, Thisted RA, et al. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry* 1992;49:651-68, discussion 69-70.
31. Robillard R, Naismith S, Smith K, et al. Sleep-wake cycle in young and older persons with a lifetime history of mood disorders. *PLoS ONE* 2014;9:e87763.
32. Haug HJ, Wirz-Justice A, Rossler W. Actigraphy to measure day structure as a therapeutic variable in the treatment of schizophrenic patients. *Acta Psychiatr Scand Suppl* 2000;(407):91-5.
33. Berle JO, Hauge ER, Oedegaard KJ, et al. Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. *BMC Res Notes* 2010;3:149.
34. Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disord* 2005;7:176-86.
35. Salvatore P, Ghidini S, Zita G, et al. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. *Bipolar Disord* 2008;10:256-65.
36. Scott E, Naismith SL, Whitwell BG, et al. Delivering youth-specific mental health services: the advantages of a collaborative, multidisciplinary system. *Australas Psychiatry* 2009;17:189-94.
37. Scott EM, Hermens DF, Glozier N, et al. Targeted primary care-based mental health services for young Australians. *Med J Aust* 2012;196:136-40.
38. Respironics P. Equivalence of activity recordings and derived sleep statistics; Actiwatch-64, Actiwatch 2 and Actiwatch Spectrum. 2009. Available: http://actigraphy.respironics.com/downloads/AWDataEquivalenceReport_0309_final.ppd (accessed 2014 Jul 24).
39. Ohayon MM, Roberts RE, Zulley J, et al. Prevalence and patterns of problematic sleep among older adolescents. *J Am Acad Child Adolesc Psychiatry* 2000;39:1549-56.
40. Marler MR, Gehrman P, Martin JL, et al. The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. *Stat Med* 2006;25:3893-904.
41. Quade D. Rank analysis of covariance. *J Am Stat Assoc* 1967;62:1187-200.
42. Robillard R, Naismith SL, Rogers NL, et al. Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *Eur Psychiatry* 2013;28:412-6.
43. Naismith SL, Hermens DF, Ip TK, et al. Circadian profiles in young people during the early stages of affective disorder. *Transl Psychiatry* 2012;2:e123.
44. Hamner MB, Diamond BI. Plasma dopamine and norepinephrine correlations with psychomotor retardation, anxiety, and depression in non-psychotic depressed patients: a pilot study. *Psychiatry Res* 1996;64:209-11.
45. Auer DP, Putz B, Kraft E, et al. Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry* 2000;47:305-13.

46. Bergink V, van Megen HJ, Westenberg HG. Glutamate and anxiety. *Eur Neuropsychopharmacol* 2004;14:175-83.
47. Lisman JE, Coyle JT, Green RW, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci* 2008;31:234-42.
48. Wulff K, Porcheret K, Cussans E, et al. Sleep and circadian rhythm disturbances: multiple genes and multiple phenotypes. *Curr Opin Genet Dev* 2009;19:237-46.
49. Ho AP, Gillin JC, Buchsbaum MS, et al. Brain glucose metabolism during non-rapid eye movement sleep in major depression. A positron emission tomography study. *Arch Gen Psychiatry* 1996;53:645-52.
50. Perlis ML, Giles DE, Buysse DJ, et al. Which depressive symptoms are related to which sleep electroencephalographic variables? *Biol Psychiatry* 1997;42:904-13.
51. Staner L, Cornette F, Maurice D, et al. Sleep microstructure around sleep onset differentiates major depressive insomnia from primary insomnia. *J Sleep Res* 2003;12:319-30.
52. Forbes EE, Williamson DE, Ryan ND, et al. Peri-sleep-onset cortisol levels in children and adolescents with affective disorders. *Biol Psychiatry* 2006;59:24-30.
53. Rao U, Dahl RE, Ryan ND, et al. The relationship between longitudinal clinical course and sleep and cortisol changes in adolescent depression. *Biol Psychiatry* 1996;40:474-84.
54. Rosen LN, Rosenthal NE, Van Dusen PH, et al. Age at onset and number of psychotic symptoms in bipolar I and schizoaffective disorder. *Am J Psychiatry* 1983;140:1523-4.
55. Dunayevich E, Keck PE Jr. Prevalence and description of psychotic features in bipolar mania. *Curr Psychiatry Rep* 2000;2:286-90.
56. Yildiz A, Sachs GS. Age onset of psychotic versus non-psychotic bipolar illness in men and in women. *J Affect Disord* 2003;74:197-201.
57. Lamont EW, Coutu DL, Cermakian N, et al. Circadian rhythms and clock genes in psychotic disorders. *Isr J Psychiatry Relat Sci* 2010;47:27-35.
58. Krystal AD, Thakur M, Roth T. Sleep disturbance in psychiatric disorders: effects on function and quality of life in mood disorders, alcoholism, and schizophrenia. *Ann Clin Psychiatry* 2008;20:39-46.
59. Bromundt V, Koster M, Georgiev-Kill A, et al. Sleep-wake cycles and cognitive functioning in schizophrenia. *Br J Psychiatry* 2011; 198:269-76.
60. Naismith SL, Norrie L, Lewis SJ, et al. Does sleep disturbance mediate neuropsychological functioning in older people with depression? *J Affect Disord* 2009;116:139-43.
61. Waters F, Sinclair C, Rock D, et al. Daily variations in sleep-wake patterns and severity of psychopathology: a pilot study in community-dwelling individuals with chronic schizophrenia. *Psychiatry Res* 2011;187:304-6.
62. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. *Am J Psychiatry* 1995;152:967-72.
63. Hickie IB, Rogers NL. Novel melatonin-based therapies: potential advances in the treatment of major depression. *Lancet* 2011;378:621-31.
64. Hickie IB, Naismith SL, Robillard R, et al. Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. *BMC Med* 2013;11:79.
65. Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. *J Psychiatr Res* 2006;40:700-8.
66. Scott EM, Robillard R, Hermens DF, et al. Sleep-wake patterns are dysregulated during early stages of major mental disorders. *J Affect Disord* 2013;145:260-3.