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Short communication

Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: Comparison of unipolar and bipolar phenotypes

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ABSTRACT

This study evaluated the potential of circadian measures as early markers of mood disorders subtypes. Patients with bipolar disorders had significantly lower levels and later onset of melatonin secretion than those with unipolar depression. Furthermore, abnormal phase angles between sleep, melatonin and temperature were found in several patients.

1. Introduction

There is widespread recognition of the premature death and disability attributable to mood disorders [17,12]. Earlier identification of those who are at risk of a bipolar-type illness is especially critical since these individuals appear to have a less consistent response to conventional antidepressant therapies and may experience the social and neurobiological harm resulting from the development of frequent depressive and manic/hypomanic episodes [1,4,10,24,28,29]. Previous work has attempted to characterize biometric characteristics of older subjects with well-established bipolar disorders [19,21,20]. However, the search for specific markers that clearly differentiate bipolar disorders from other unipolar phenotypes *early in the illness course* has yielded limited results [4,10,6,9,8,11].

In recent years, there has been increasing attention on circadian systems and their relationships with the onset, course and response to treatment of mood disorders. Melatonin and core body temperature (CBT) follow robust circadian rhythms. Abnormally flat circadian amplitude and disturbed timing of melatonin rhythms have been observed in people with depression [18,5,14,22]. Furthermore, misalignment between melatonin, CBT and sleep timing has recently been shown to correlate with depression severity in a mostly middle aged sample of patients with unipolar depression [13] and shifting the circadian phase to earlier times has been found to reduce depressive symptoms [15,16]. Melatonin and its relative alignment with CBT and sleep are thus interesting marker candidates for the early stages of mood disorders.

In line with a series of studies aiming to better characterise the interplay between circadian rhythms and various aspects of early stage psychiatric phenotypes [23,25,27], this preliminary study investigates the potential of circadian measures as markers of mood disorders and their polarity in young people.

2. Subjects and methods

2.1. Participants

Thirty-two patients between 15 and 30 years of age (eight males and 24 females) seeking professional help primarily for significant depressive symptoms were recruited from specialised services for mental health problems in young people (Youth Mental Health Clinic at the Brain and Mind Research Institute; and headspace, Campbelltown, Sydney, Australia). None of them had done shiftwork or travelled across more than two time zones in the 60 days prior to the experimental protocol. Twenty-four patients were medicated for their mood disorder (13 from the unipolar group and 11 from the bipolar group, Table 2). The study protocol

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

2.2. Clinical assessment

An independent psychiatrist or trained research psychologist conducted a standard clinical interview and defined unipolar/bipolar subtypes based on the history of manic/hypomanic episodes (DSM-IV criteria). Diagnoses were subsequently confirmed by consensus of the senior investigators (IBH and ES). Eighteen patients were diagnosed with unipolar depression and 14 patients were diagnosed with bipolar depression (see Table 1 for demographic characteristics). All patients were in a depressive episode at the time of assessment. Depression severity was assessed via self-report using the Beck Depression Inventory II (BDI-II) [2].

2.3. Circadian assessment

Actigraphic data acquired every 30 second over 7 consecutive days/nights (Actiwatch-64, Philips Respironics, USA) was used to determine habitual sleep schedule. Sleep onset/offset times were automatically defined with the Actiware 5.0 software (Philips Respironics, USA) and further inspected visually.

Following actigraphy monitoring, saliva samples were collected using Salivettes (Sarstedt, Germany) every 30 minutes for eight hours, starting six hours before individual habitual bedtimes. Patients remained awake and sited in dim light (<50 lux). Melatonin concentrations were determined by double antibody radioimmunoassay (RKDSM2; Buhlmann Laboratories AG, Switzerland) with a detection threshold of 0.999 pg/mL (inter-assay coefficient of variation: 15% at 4.530 pg/mL and 12.3% at 41.114 pg/mL, intra-assay coefficient: $<10\%$ across the standard curve). Dim light melatonin onset (DLMO) was determined when melatonin concentration reached a threshold of 3.000 pg/mL and remained above this threshold for the next three samples. Melatonin area under the curve (AUC; trapezoid method) was calculated for each participant.

In the following week, CBT was recorded in the laboratory in a subsample of eight patients (five unipolar and three bipolar) using an ingestible sensor transmitting data wirelessly every minute (VitalSense, Philips Respironics, USA). Patients ingested the sensor at about 7 pm and slept according to their habitual schedule. CBT minimum (CBT_{min}) was visually identified by three independent technicians with a mean inter-judge difference of 13.2 minutes (SD: 16.8). The average of the three times was used for qualitative analyses.

2.4. Statistical analyses

All statistical analyses were conducted with Statistica 6.1 software (StatSoft Inc, USA). T-tests were used to assess group differences in age, BDI-II scores, sleep onset and offset times and DLMO. Mann-Whitney U tests were used for AUC and the phase angle between DLMO and $Sleep_{ON}$ because these variables were not normally distributed. Due to missing data, one participant from the unipolar group was excluded from BDI-II analyses and eight participants (five unipolar and three bipolar) were excluded from the actigraphy analyses.

3. Results

Table 1 presents mean BDI-II scores, circadian variables and statistics for each group (see Table 2 for a summary of individual data). Mean BDI-II scores were in the 'moderate depression' range for both the unipolar and bipolar groups. While there was no significant group difference in sleep onset times, sleep offset times were significantly later in the bipolar than the unipolar group.

Melatonin concentrations did not reach the threshold for DLMO before the end of saliva sampling for eight patients (four from each subgroup). For analyses purposes, the DLMO of these patients was considered to occur 30 minutes after the last sample. Compared to the unipolar group, the bipolar group had later DLMO and smaller melatonin AUC than the unipolar group (Fig. 1).

In total, 10 patients (five unipolar and five bipolar) had an abnormal phase angle between the melatonin and sleep rhythms, with DLMO occurring after mean actigraphic sleep onset time or DLMO not occurring before the end of data collection (i.e. two hours after habitual sleep onset). There was no significant group difference in the phase angle between melatonin and sleep onset time. Negative phase angles between CBT_{min} and sleep midpoint were found in five of the eight patients with temperature data (Fig. 2).

4. Discussion

The current results suggest that evening melatonin onset is reduced and delayed in a great proportion of young people with mood disorders, and that these abnormalities are more prominent in those with bipolar compared to unipolar depression.

Despite the absence of a control group, this study highlights significant abnormalities in the usual relation between the timing of melatonin secretion and sleep. In one third of our patients, DLMO occurred after (rather than before) habitual sleep onset.

Table 1
Depression and circadian variables by group.

	Unipolar	Bipolar	t/U	*p*
Age, years	21.8 (4.3)	22.8 (4.8)	−0.59	0.560
Individuals under 19 y.o.	*n* = 3, 23.0%	*n* = 3, 21.4%	–	
Gender, females	*n* = 13, 72.2 %	*n* = 11, 78.6 %	–	
BDI-II score	22.4 (12.0)	22.4 (11.2)	0.01	0.991
DLMO[a]	22:55 (1:56)	24:38 (2:35)	2.16	0.039
AUC, pg/mL/min[a]	2013.4 (1509.7)	1029.6 (745.6)	72.0	0.040
$Sleep_{ON}$[b]	23:52 (1:06)	24:58 (2:14)	1.57	0.131
$Sleep_{OFF}$[b]	8:45 (1:11)	10:37 (2:06)	2.73	0.012
CBT_{min}[c]	4:38 (1:12)	6:09 (2:02)	–	
∠ $Sleep_{ON}$–DLMO[b]	1.2 (1.6)	0.6 (1.5)	53.0	0.284
∠ CBT_{min}–Midpoint[c]	−0.3 (1.5)	−0.2 (1.4)	–	
∠ CBT_{min}–DLMO[c]	6.2 (1.8)	5.7 (2.4)	–	

Means (standard deviations). ∠: Phase angle (in hours); AUC: melatonin area under the curve; BDI: Beck Depression Inventory; CBT: core body temperature; DMLO: dim light melatonin onset CBT_{min} reported for descriptive purposes as the sample was too small for statistical analyses.

[a] $n_{Unipolar} = 18$ and $n_{Bipolar} = 14$

[b] $n_{Unipolar} = 13$ and $n_{Bipolar} = 11$

[c] $n_{Unipolar} = 5$ and $n_{Bipolar} = 3$.