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Schizophrenia patients with predominantly positive symptoms have more disturbed sleep–wake cycles measured by actigraphy

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ABSTRACT

Sleep disturbances are widespread in schizophrenia, and one important concern is to determine the impact of this disruption on self-reported sleep quality and quality of life (QoL). Our aim was to evaluate the sleep–wake cycle in a sample of patients with schizophrenia (SZ), and whether sleep patterns differ between patients with predominantly negative versus predominantly positive symptoms, as well as its impact on sleep quality and QoL. Twenty-three SZ outpatients were studied with 24 h continuous wrist-actigraphy during 7 days. The quality of sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI), and the self-reported QoL was evaluated with the World Health Organization Quality of Life – Abbreviated version (WHOQOL-Bref). About half of the studied population presented an irregular sleep–wake cycle. We found a trend for more disrupted sleep–wake patterns in patients with predominantly positive symptoms, who also had a trend self-reported worse quality of sleep and worse QoL in all domains. Overall, patients with worse self-reported QoL demonstrated worse sleep quality. Our findings suggest that SZ patients are frequently affected with sleep and circadian rhythm disruptions; these may have a negative impact on rehabilitation strategies. Moreover, poor sleep may play a role in sustaining poor quality of life in SZ patients.

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1. Introduction

Sleep is an important restorative physiologic process (Suresh Kumar et al., 2007). The sleep–wake cycle is a circadian rhythm generated and regulated by the suprachiasmatic nucleus of the hypothalamus, synchronized by internal (body) and external (environment) stimuli (Albrecht, 2002; Van Gelder, 2004).

Patients with schizophrenia (SZ) frequently experience sleep problems (Keshavan et al., 1990; Taylor et al., 1991; Tandon et al., 1992; Monti and Monti, 2004; Cohrs, 2008), like advanced sleep phase syndrome and hypersomnia with short naps (Wirz-Justice et al., 2001). Reduced sleep efficiency and total sleep time, increased sleep latency, decrease in slow wave sleep (SWS) and rapid eye movement (REM) latency have also been reported in most patients with SZ (Tandon et al., 1992; Zarcone et al., 1987; Keshavan et al., 1998). This is especially true during psychotic episodes (Kupfer et al., 1970), but also in the prodromal phase (Donlon and Blacker, 1975; Cohrs, 2008).

It remains unclear whether sleep problems in SZ are secondary to social withdrawal and reclusive behavior, to medication, or to an abnormality of the neuroendocrine systems regulating sleep and wakefulness (Wulff et al., 2006).

Although sleep architecture improves with antipsychotic treatment, sleep remains mostly fragmented and fails to establish its normal pattern (Kupfer et al., 1970). This suggests that sleep physiology might share a common substrate with SZ symptoms (Boivin, 2000; Poulin et al., 2003; Cohrs, 2008). Furthermore, worse sleep quality has been associated with poorer quality of life (QoL), even after correcting for depression and drug effects (Hofstetter et al., 2005; Ritsner et al., 2004). Positive and negative symptoms, neurocognitive impairment and brain structure may also correlate with important sleep variables such as sleep latency, sleep efficiency, SWS, and REM sleep parameters (Cohrs, 2008). REM density was inversely correlated with positive, cognitive, and emotional discomfort symptoms as well as the total score on the Positive and Negative Syndrome Scale (Yang and Winkelman, 2006).

However, because of the limited number of methodologically rigorous studies, no clear statement can be made about the influence of these variables on sleep structure (Cohrs, 2008). Actigraphy has been used in SZ to study sleep and circadian rhythms (Haug et al., 2000; Poyurovsky et al., 2000; Shamir et al., 2000; Hofstetter et al., 2005; Martin et al., 2005; Wulff et al., 2006), but studies have been limited, probably for methodological feasibility reasons (Vanelle, 2009).

One of the most important goals in SZ treatment is social and professional rehabilitation. To accomplish this, physiologic sleep, compatible with work routines and timetables is necessary.

We aimed to evaluate the sleep–wake cycle in a sample of SZ patients, and whether sleep patterns differed between patients with predominantly negative versus predominantly positive symptoms.

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Moreover, we hypothesized that worse quality and sleep patterns, would be associated with poorer self-reported QoL.

2. Material and methods

2.1. Participants

Data herein reported is based on an ongoing investigation on sleep characteristics of SZ patients at Lisbon's Psychiatric Hospital Center. Twenty-three patients with SZ, aged 19–52 yrs, were diagnosed according to DSM-IV criteria (APA, 2000), ascertained from interview with a psychiatrist and medical chart review. Patients were evaluated with the Positive and Negative Syndrome Scale – PANSS (Kay et al., 1989). Based on the PANSS scores, patients were divided into two groups according to symptom preponderance: Group 1 (n = 11) included patients with predominant positive symptoms, and Group 2 (n = 12) included patients with predominant negative symptoms.

At the time of evaluation all patients had been on a stable medication regimen for at least 1 month. Patients taking benzodiazepines in daily doses lower than the equivalent of diazepam 15 mg (never taken after 18h00) were accepted. A minimum washout period of 72 h was obligatory for hypnotic medication. The daily dosage of antipsychotics and diazepam used in each treatment group was as follows. (1) Group 1: olanzapine (n = 4), mean 18.8 mg; quetiapine (n = 1), mean 600 mg; risperidone (n = 3), mean 6 mg; clozapine (n = 3), mean 367 mg; diazepam (n = 2) mean 7.5 mg; (2) Group 2: olanzapine (n = 4), mean 17.5 mg; quetiapine (n = 1), mean 400 mg; risperidone (n = 2), mean 4.5 mg; clozapine (n = 4), mean 362.5 mg; ziprasidone (n = 1), mean 120 mg; diazepam (n = 3) mean 8.3 mg.

Schizoaffective disorder, organic impairment, previous head trauma or neurological disorders, or substance abuse/dependence were considered exclusion criteria. Patients working night-shifts were also excluded.

The local Ethics committee approved the study, and all participants provided written informed consent.

2.2. Assessment instruments

The quality and patterns of sleep were measured with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). This self-report questionnaire rates sleep quality and patterns during the previous month, and evaluates 7 components of sleep: subjective quality, latency, duration, usual efficiency, sleep disturbances, medication use, and daytime dysfunction. The score is given through a Likert-like scale, between 0 and 3, with a cut-off value of 5, higher scores meaning worse sleep quality.

Subjective quality of life (QoL) was assessed using the WHO Quality of Life Measure – Abbreviated version (WHOQOL–BREF–PT), Portuguese version. The 26-item version WHOQOL–BREF (W.H.O.Q.O.L. Group, 1994) provides measurement on four domains: physical, psychological, social relationships, and environment. Higher scores mean better QoL.

Wrist-actigraphy was used for sleep–wake cycle assessment. Actigraphy provides the recording of continued limb motor activity during 24 h or longer periods and is a useful and validated instrument for sleep studies (Ancoli-Israel et al., 2003). Actimeters (SomnoWatch® actigraphy system) were strapped on the patients' nondominant wrists. Movement counts of the actigraph were stored in 1 second interval, with the signal sampled at 32 Hz with 12 Bit ADC, allowing continuous recording for 168 h (7 days) on the 16 MB memory. We chose the smallest possible interval to achieve maximum temporal resolution. Since actigraphy cannot distinguish between sleep and sedentary activities, subjects recorded in a diary, bed and wake times, awakenings at night, day naps, and other activities. During the study period all participants used the equipment at all times, except when bathing. In these situations we asked the participants to mark this period by pressing a button to mark events on the SomnoWatch® (before and after bathing). Data during these periods were treated as missing.

2.3. Sleep/wake variables and actigraphic parameters

Sleep latency was considered as the time period between turning-off the light and falling asleep. The actigraph contains a light sensor that measures the time between the instant when the light goes off and the reduction of motor activity (typical of sleep onset). To score sleep onset we used the 5 min of actigraphic immobility criterion (Chae et al., 2009). To assess sleep–wake cycles the actogram was visually analysed and confronted with the sleep log information given by the patients. The sleep–wake rhythm was considered regular when there was a clear distinction between sleep/inactivity occurring at night and wake/activity periods occurring during the day, and regular occurrences of both during the week.

Using the sleep log information, and the light sensor information, we divided the data between night (period between lights off and wake) and day period. Data were transferred to our own EXCEL® templates for further analyses. We chose to extract three variables from the data that had previously been described (Middelkoop et al., 1997). Actigraphy measures were calculated as follows:

- (i) movement index (MI) (%), indicating the percentage of epochs with an activity count >0.
- (ii) activity level (AL), number of activity counts per hour.

Table 1
Sociodemographic and clinical characteristics.

Characteristics	Group 1 (N = 11) (predominant positive symptoms)	Group 2 (N = 12) (predominant negative symptoms)	Chi ²
	mean (S.D.)	mean (S.D.)	p-value
Gender (men:women)	9:2	10:2	0.925
Age	37.2 (10.2)	39.8 (9.7)	0.459
Employed	5	0	0.010*
Educational level (yrs)	9.4 (2.7)	8.8 (3.1)	0.550
Illness duration (yrs)	13.4 (8.7)	15.6 (9.4)	0.517
Number of admissions	2.1 (1.9)	2.8 (2.4)	0.409

Legend: yrs: years; S.D.: standard deviation.
* p < 0.05.

(iii) mean duration (s) of uninterrupted immobility (MIP)(activity = 0). The mean duration of uninterrupted immobility periods (MIP) provides a global measure of the distribution and number of immobility periods.

2.4. Statistical analysis

Both groups were compared in sociodemographic, and clinical variables using nonparametric Mann–Whitney test, Chi-Square and contingency (symmetry). Correlations of sociodemographic and clinical variables, WHOQOL–BREF, PSQI, and actigraphy data were calculated through Spearman correlation. We used SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Social, demographic, and clinical characteristics of our sample are presented in Table 1. Significant statistical differences were found only in professional activity, patients with preponderant negative symptoms being all inactive.

There was no difference in PANSS total (Group 1, mean 89.4, S.D. 19.3; Group 2, mean 82, S.D. 22.6) or general psychopathology results between both groups (Group 1, mean 48.5, S.D. 10.5; Group 2, mean 44, S.D. 11.0). Because of the patients' allocation, the positive symptom's PANSS subscale results were higher in Group 1 (mean 24.2, S.D. 5.4) than in Group 2 (mean 12.3, S.D. 3.2). On the other hand, negative symptom's PANSS subscale results were higher in the latter (mean 26.1, S.D. 9.2) than in Group 1 (mean 16.6, S.D. 5.2). For these results, there was statistical significance.

Both groups presented a score above of 5 on the PSQI, which is considered as poor sleep quality (Table 2). Group 2 subjects self-reported better QoL in all domains, compared to Group 1, but the differences were not statistically significant (Table 2).

No significant differences were found in motor activities measurements during wakefulness (day) and sleep (night) between the two groups (Table 3).

Table 2
Quality of sleep and quality of life in both patient groups.

Scales	Group 1 (N = 11) (predominant positive symptoms)	Group 2 (N = 12) (predominant negative symptoms)	Mann–Whitney Test p-value
Quality of sleep			
PSQI total	7.7 (5.1)	6.2 (3.8)	0.535
Quality of life			
WOQOL – physical domain	61.0 (14.1)	63.4 (17.3)	0.663
WOQOL – psychological domain	50.0 (16.6)	56.0 (16.3)	0.419
WOQOL – social domain	40.4 (20.7)	53.1 (19.0)	0.137
WOQOL – environmental domain	59.7 (17.5)	62.2 (16.4)	0.618

Legend: PSQI: Pittsburgh Sleep Quality Index; WHOQOL: World Health Organization Quality of Life.

Table 3
Actigraphy results between the patient groups.

Variables	Group 1 (predominant positive symptoms)		Group 2 (predominant negative symptoms)		p-value ^a
	Mean	S.D.	Mean	S.D.	
Sleep latency (min)	51.2	29.9	38.8	25.0	0.325
Movement index (%)					
Day	65.2	13.3	57.0	15.5	0.140
Night	12.7	12.3	19.8	17.5	0.356
Activity level (number of counts/hour)					
Day	101084.3	64716.7	91828.7	43579.8	0.806
Night	17046.6	14393.2	16184.0	7505.6	0.622
Uninterrupted immobility duration (s)					
Day	18.0	15.5	20.0	17.2	0.902
Night	160.4	201.6	72.8	60.6	0.325
Regular sleep–wake rhythm	N = 4 (36%)	–	N = 8 (67%)	–	0.146 ^b

Legend: min: minutes; s: seconds; S.D.: standard deviation.

^a Mann–Whitney test.

^b Chi-square test.

Group 1 presented worse actigraphy patterns with 7 patients (64%) presenting an irregular sleep–wake cycle (Fig. 2) and only 4 patients showing regular sleep–wake cycles (Table 3 and Fig. 1). Sleep latency was higher in Group 1 (Table 3), but these differences were not statistically significant. Only 36% of Group 1 patients presented normal alternation between sleep/wake states, as compared to 67% in Group 2; however, these differences were not statistically significant. In Group 2, 4 patients (33%) presented irregular sleep–wake pattern, while 8 showed regular sleep–wake cycles; these differences were not significant ($\chi^2 = 2.112$; $p = 0.220$), but the contingency analysis showed symmetry among them ($p = 0.146$).

Significant negative correlations were found between PANSS subscales' scores and WHOQOL-BREF and PSQI scores, indicating that higher symptom levels correlate with lower self-reported QoL and worse quality of sleep (Table 4). However, we found no significant correlations between sleep/wake variables and quantitative motor activity on actigraphy, and scores on any PANSS subscales, and/or any QoL domain (data not shown).

4. Discussion

Our results show that there is a trend for more disrupted sleep–wake patterns and circadian activity rhythms in SZ patients with predominant positive symptoms. In fact, Group 1 patients self-reported worse quality of sleep as compared to Group 2, except for one item (hypnotic use). Moreover, Group 1 patients self-reported worse QoL in all domains as compared to patients with predominant negative symptoms, indicating that worse sleep patterns may lead to worse subjective quality of sleep and QoL. Our results support previous findings that SZ patients show more disrupted sleep–wake patterns and circadian activity compared to healthy subjects (Martin et al., 2005).

An important aspect in actigraphy results was sleep latency; in both groups sleep latency proved to be quite long (usually, sleep latency should take about 30 min), as confirmed by the patients' subjective opinion of worse quality of sleep.

We found differences, although not statistically significant, between the groups regarding regular sleep–wake rhythms; 11 out of 23 subjects showed an irregular sleep–wake rhythm. We verified a relative absence of a circadian pattern of the sleep–wake cycle. The actogram and the sleep log showed that sleep times were randomly distributed throughout the day and night and sleep duration and wake-up episodes were variable and unpredictable during the 24 h period. Actigraphy confirmed daytime napping and nighttime fragmentation, a common finding in SZ patients (Yamadera et al., 1996).

We found a significant association between psychopathology and general symptoms, and quality of sleep, but no significant correlations with positive and negative symptoms, and quality of sleep. Other symptoms, namely depressive, could possibly influence more the quality of sleep, than positive or negative symptoms. We were able to replicate earlier findings showing that in schizophrenia self-reported QoL is associated with quality of sleep (Ritsner et al., 2004; Hofstetter et al., 2005; Xiang et al., 2009). In our sample, patients with predominant negative symptoms reported better quality of sleep and better QoL. Patients with negative syndrome present low motor activity levels (Walther et al., 2009), possibly facilitating sleep. On the other hand, hallucinations and delusions may cause difficulty in falling

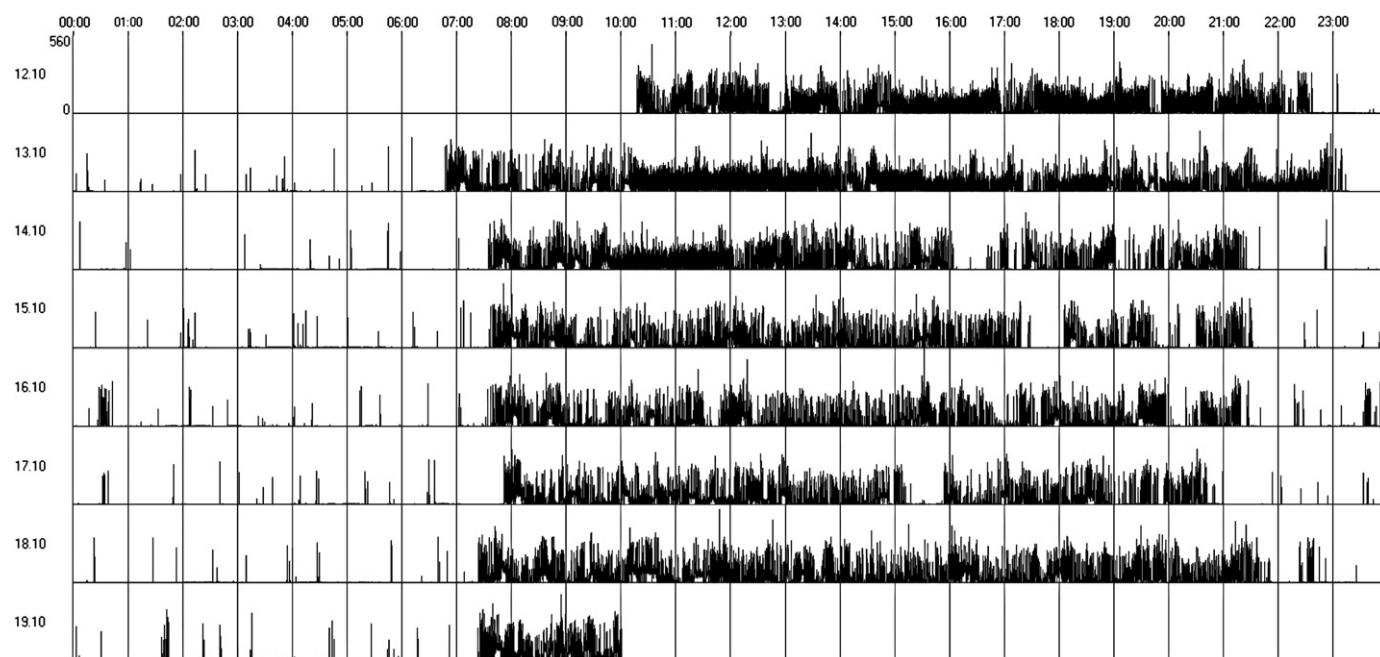


Fig. 1. Regular sleep–wake rhythm (actogram obtained by actigraphy over a 7-day period).

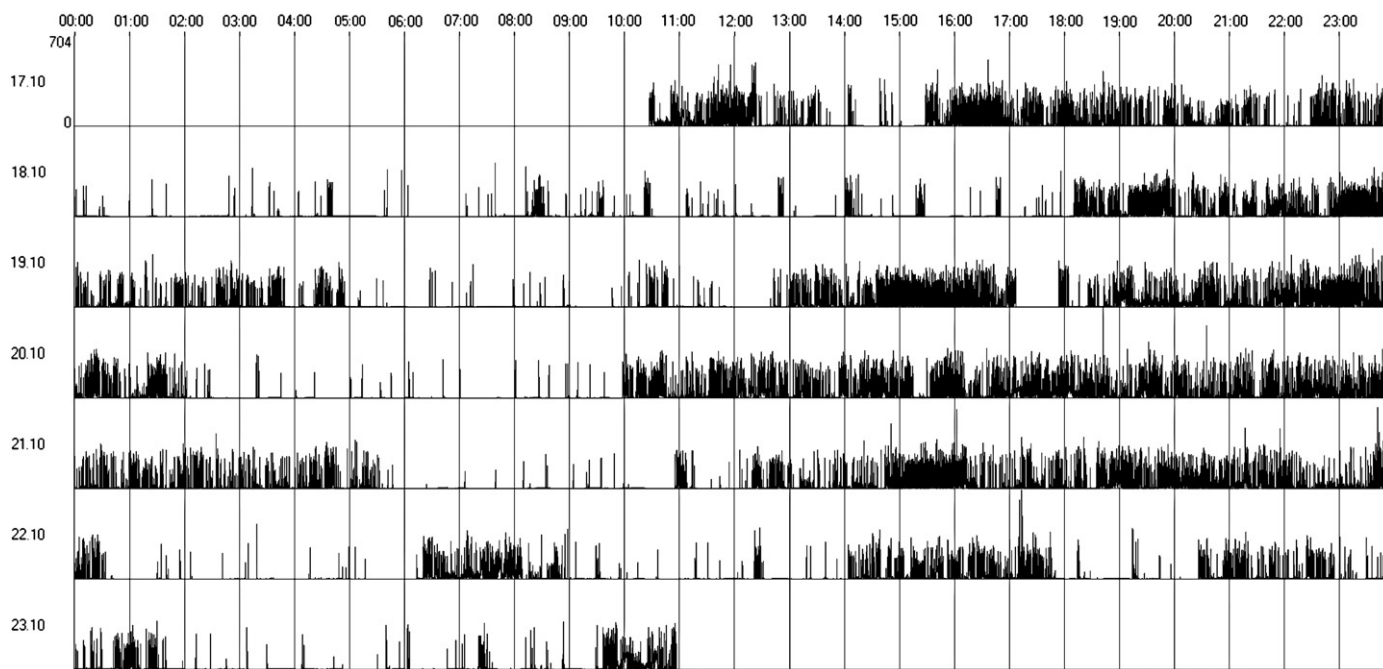


Fig. 2. Irregular sleep-wake rhythm (actogram obtained by actigraphy over a 7-day period).

asleep, and thereby having a negative impact on both sleep quality and QoL.

Evidence shows that when circadian rhythm sleep is disturbed, daytime sleepiness, insomnia, and displacement of social timetables occur (APA, 2000). This contributes negatively to rehabilitation interventions. Interestingly, we found an association between having a daily occupation, and better sleep quality and lower sleep latency, indicating that social and professional rehabilitation could reflect positively in the patients' circadian rhythms.

Unexpectedly, we found no significant correlations between psychopathology, self-reported QoL and quality of sleep, and sleep/wake variables registered by actigraphy, possibly due to the small sample size. Also, our sample consisted of rather symptomatic patients, possibly with low insight into their quality of sleep and QoL.

Atypical antipsychotics tend to improve sleep induction and/or sleep maintenance in SZ patients (Monti and Monti, 2004), and most atypical antipsychotics demonstrate an increase in total sleep time and/or sleep efficiency in SZ patients, with the exception of risperidone (Cohrs, 2008). To disentangle the effects of schizophrenia itself from the influence of medication on sleep is difficult (Cohrs, 2008), but it seems unlikely that treatment only could explain the differences between the groups.

The causes for the present findings remain unknown. The tendency for more daytime inactivity sleepiness periods in Group 2 patients may be explained by social withdrawal, reclusive behavior, and low motor activity levels associated with the negative syndrome (Walther et al., 2009). On the other hand, positive symptoms, namely suspiciousness, hallucinations and hyperactivity, could make it harder for the patients to fall asleep, due to an increased neurophysiologic arousal, explaining the longer sleep latency, and lower total sleep time found in this group.

Another good candidate to explain changes in the sleep-wake rhythm is melatonin, a hormone produced by the pineal gland, and an endogenous synchronizer of circadian rhythms. Nocturnal plasma melatonin levels have been reported to be reduced in SZ patients as compared with normal controls (Shamir et al., 2000; Viganò et al., 2001; Mann et al., 2006; Suresh Kumar et al., 2007), probably due to changes of the pineal gland (Sandyk et al., 1990). Some theories have proposed that SZ is caused by a damage produced in utero, to zinc dependent

fetal organs such as the brain and pineal gland (Richardson-Andrews, 2009). Moreover, lesions of the suprachiasmatic nucleus have been postulated to play an important role in the aetiology of SZ (Trbovic, 2010). Therefore, future studies should explore the relation between sleep-wake cycles and melatonin levels in SZ patients.

The inclusion of patients who were taking benzodiazepines before 18h00 is a study limitation, since activity levels are significantly reduced following an acute administration of lorazepam 2.5 mg (Dawson et al., 2008). Despite that, in our sample all the 4 patients had been taking diazepam (medium dose = 8 mg) for long-term. Our patients presented elevated symptom levels, and therefore our results may not be applicable to patients in remission.

Previous studies reported lower quantitative motor activity parameters than those of the present study (Walther et al., 2009; Farrow et al., 2005; Farrow et al., 2006). This can probably be explained by differences in algorithms used for calculation of activity and by differences between the actigraphs, since they have different sensor types, sampling rates and storage rates. Furthermore, the American Academy of Sleep Medicine (AASM) referred some problems when comparing actigraphy data. According to the "AASM Standards and Practice", additional research is needed which compares results from different actigraphy devices and the variety of algorithms used to evaluate actigraphy data in order to further establish standards of actigraphy technology (Morgenthaler et al., 2007).

Quantitative motor activity parameters during wakefulness were related to the clinically assessed negative syndrome in schizophrenia (Walther et al., 2009). In our study we didn't replicate these findings, probably because of the small sample size. Furthermore, we didn't find a relation between motor activity parameters and sleep-wake rhythm. This could be explained by the fact that schizophrenia is a heterogeneous disease with significant differences in activity or immobility periods. Therefore, the volume of specific executive brain structures may affect motor behaviors. Cumulative motor activity over a 20 h period was correlated with the volume of left anterior cingulate cortex in schizophrenia patients (Farrow et al., 2005).

Finally, our results are preliminary and due to the small sample size, and lack of a control group, need further replication.

In summary, our findings show a trend for more disrupted sleep-wake patterns and circadian activity rhythms in SZ patients with

predominant positive symptoms; these patients also self-reported worse quality of sleep and worse QoL in all domains as compared to patients with predominant negative symptoms.

These circadian abnormalities may reinforce the altered sleep patterns, cognitive problems, and social engagement, with a negative impact on rehabilitation strategies. Moreover, our results support the hypothesis that poor sleep may worsen QoL in SZ patients. In clinical practice, psychiatrists should give more attention to sleep complaints in schizophrenia since that can have a negative impact in the quality of life of these patients.

Conflict of interest

The authors report no conflict of interest. Dr. Sofia Brissos is consultant for Janssen-Cilag Portugal.

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