Sleep Architecture in Schizophrenia Patients

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SUMMARY

Objective: Sleep disorders are a common and important part of schizophrenia's clinical Picture; however, the number of polysomnography-based studies of schizophrenia is limited and there is a lack of consensus regarding a specific sleep pattern in schizophrenia patients. As such, the aim of the present study was to investigate the sleep architecture in non-medicated schizophrenia patients.

Method: The study included 13 adult male inpatients with schizophrenia, undifferentiated type, (based on DSM-IV-TR criteria) and an age- and sex-matched group of normal controls. The participants were studied during 2 consecutive nights in the sleep laboratory. The Brief Psychiatric Rating Scale (BPRS), Scale for Negative Symptoms (SANS), and Scale for Positive Symptoms (SAPS) were used for clinical assessment. Polysomnographic recordings obtained on the second night were used for analysis.

Results: Compared to the controls, the schizophrenic patients had less total sleep time, lower sleep efficiency, longer sleep latency, more awakenings, and increased duration of awakenings after falling asleep. In terms of sleep architecture, the schizophrenia patients showed no evidence of abnormal-slow wave sleep, but the percentage of REM sleep was reduced. REM sleep measures, including REM latency and density, did not significantly differ between the 2 groups. Based on correlation analysis between the sleep parameters and clinical symptoms, slow-wave sleep was inversely correlated with formal thought disorder.

Conclusion: The findings indicate that in addition to decreased REM sleep time, disturbances in sleep initiation and maintenance were prominent in the non-medicated schizophrenia patients. The correlation between decreased decreased REM sleep and, slow-wave sleep, and formal thought disorder we observed in the patients might have been related to the underlying pathophysiology of schizophrenia.

Key Words: Schizophrenia, sleep, sleep structure, polysomnography.

INTRODUCTION

Sleep disturbances are common in schizophrenia patients and are usually an important part of the clinical picture during periods of exacerbation. When the clinical picture remits, sleep disturbances, such as sleep-wake disturbances due to abnormal sleep-wake patterns and insomnia, also persist (Haffmans 1994).

Sleep research provides an opportunity to analyze the sleep architecture and changes in the sleep stages at the macro and micro level. Such research has provided a different perspective for clarifying the pathophysiology of schizophrenia within the dimensions of sleep physiology (Krystal et al. 2006). Several sleep studies have been performed with schizophrenia patients in an effort to understand the pathophysiology of schizophrenia; however, a specific sleep pattern associated with schizophrenia has not been described. The most consistently reported polysomnographic findings in these studies relate to changes in sleep initiation and maintenance, such as reduced total sleep time (Tandon et al. 1992; Lauer et al. 1997; Keshavan et al. 1998), prolonged sleep latency (Jus et al. 1973; Kempenaers et al. 1988; Benson et al. 1991;

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1996; Van Cauter et al. 1991; Poulin et al. 2003; Yang and Winkelman 2006), and poor sleep efficiency (Benson and Zarcone 1993, Hudson et al. 1993, Nishino et al. 1998, Yang and Winkelman 2006).

Older sleep studies were performed based on the hypothesis that there is a possible link between hallucinations and abnormal REM sleep; however, inconsistent results were obtained regarding REM sleep variables (particularly REM latency and REM density). Some studies reported reduced REM latency in patients with schizophrenia (Jus et al. 1973; Benson et al. 1991; 1993; Tandon et al. 1992; Hudson et al. 1993; Röschke et al. 1998; Poulin et al. 2003), whereas other sleep studies did not support this finding (Gaillard et al. 1984; Ganguli et al. 1987; Lauer et al. 1997; Keshavan et al. 1998; Hoffmann et al. 2000; Sekimoto et al. 2006; Yang and Winkelman 2006). Most studies that examined REM density did not report any differences between schizophrenics and normal controls (Ganguli et al. 1987; Lauer et al. 1997; Keshavan et al. 1998; Poulin et al. 2003; Yang and Winkelman 2006), yet some studies reported a correlation between positive symptoms and REM density (Benson and Zarcone 1993; Yang and Winkelman 2006).

Findings related to slow-wave sleep (stage 3 and 4 sleep) abnormalities have also been inconsistent. Some studies reported decreased slow-wave sleep (Benson et al. 1991; 1996; Benson and Zarcone 1993; Sekimoto et al. 2006; Yang et al. 2006), while others did not observe such deficits (Ganguli et al. 1987; Kempenaers et al. 1988; Tandon et al. 1992; Hudson et al. 1993; Lauer et al. 1997; Keshavan et al. 1998; Poulin et al. 2003). Only 1 study reported that schizophrenic patients had increased slow-wave sleep (Nishino et al. 1998).

The discrepancy in findings in studies is considered to be the result of methodological shortcomings and participant heterogeneity of subjects. Moreover, patients with different subcategories of schizophrenia, and differences in illness duration, age, gender, and medications used during the studies are considered other confounding factors. In particular, use of neuroleptics is an important confounding factor, as they have profound effects on sleep architecture.

In consideration of these methodological aspects, the present study aimed to investigate the sleep architecture in a homogenous group of schizophrenia patients. In order to increase the clinical homogeneity of the study sample, only drug-free adult male patients with undifferentiated type schizophrenia were included.

METHODS

Participants

The study included schizophrenia patients admitted to the schizophrenia inpatient unit of Gülhane Military Medical Academy (GMMA), Ankara, Turkey between 2002-2006. Inclusion criteria for the patients and controls included medication-free status, independent medical disorders, and a primary sleep disorder (including sleep apnea syndrome, periodic limb movements, restless legs syndrome, parasomnia and narcolepsy) independent of the abuse of drugs or alcohol, and no use of alcohol for at least 2 weeks prior to the beginning of the study. Females were not included in the study because primary sleep disorders -including insomnia- are more common in females than in males and changes in the hormone profile associated with the menstrual cycle can have profound effects on sleep structure (Driver 2006).

In all, 16 patients that met DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia, undifferentiated type were included in the study. Ten of the patients stopped taking their medication at least 2 months earlier noncompliance with treatment. The 6 other patients had never taken psychotropic medication.

The control group consisted of 13 age- and sex- matched healthy volunteers without a history of psychiatric disorder and no history of first-degree relatives with a psychiatric disorder. None of the controls had a major medical, neurological, or primary sleep disorder.

The study protocol was fully explained to the participants and each provided written informed consent. The study protocol was approved by the GMMA Ethics Committee. Prior to beginning the study all the participants were screened for DSM Axis I psychiatric disorders using the Structured Diagnostic Interview for DSM-IV (SCID-I), (First et al. 1997; Çorapçıoğlu et al. 1999) and were screened for sleep disorders using a sleep questionnaire form.

Patients that met the inclusion criteria and agreed to participate in the study underwent sleep study during their first week of hospitalization. Among the 16 schizophrenia patients, 3 were excluded from the study because they did not complete the first night of polysomnographic recordings. 2 of them refused to continue during the first night recording because they were disturbed by the electrodes and the third patients removed his electrodes himself and left the laboratory. Thusly, the 13 patients that completed the study protocol were included in our analysis. Mean age of 13 patients was 24.4 ± 5.9 years (range: 19-36 years) versus 25.3 ± 5.0 years (range: 20-34 years) for the controls.

Assessment instruments

The severity of illness among the schizophrenic patients was assessed using the Brief Psychiatric Rating Scale (BPRS). The scale was developed by Overall and Gorham (1962) and Soykan (1989) reported that it is reliable for use with the Turkish population. The BPRS includes some rate-based items according to direct observation during the interview process and some items based on clinical observations during the previous 3 days. The BPRS has 18 items, each of which is scored from 0 - 6 points; total score is the sum of the 18 items' scores.

The Scale for Assessment of Negative Symptoms (SANS) was used to determine the severity of negative symptoms. The scale was developed by Andreasen (1983) and Erkoç et al. (1991a) reported that it is reliable and valid for use with the Turkish population. The scale contains 25 items on 5 subscales, including blunted affect, poverty of thought (alogia), apathy-avolition, anhedonia, and inattentiveness, and scored based on clinical observations during the previous week.

The Scale for Assessment of Positive Symptoms (SAPS), developed by Andreasen (1984), was used to determine the severity of positive symptoms. The scale was reported to be reliable and valid for use with Turkish population by Erkoç et al. (1991b). The 34 items on its hallucinations, delusions, bizarre behavior and formal thought disorder subscales are answered based on clinical observations during the previous week.

The sleep questionnaire form for sleep disorders used in the present study was developed for use in general sleep studies by the GMMA sleep laboratory. It was designed to screen sleep hygiene, sleep-wake habits, and sleep disorders, including insomnia, hypersomnia, parasomnia, sleep related breathing disorders, and sleep-related movement disorders (restless legs syndrome, periodic limb movement, bruxism).

Each of the scales were administered by each patient's doctor the day of the first-night polysomnographic recording.

Polysomnographic recording and scoring

The participants underwent polysomnography on 2 consecutive nights in the sleep laboratory. Recordings were made using a 16-channel polygraph (SomnoStar Alpha Series 4, Sensormedics, Yorba Linda, CA, USA). The first night was accepted as the adaptation night, and served to screen for primary sleep disorders; therefore, on the first night of the study, full-montage polysomnograms were recorded, consisting of an electroencephalogram (EEG) (C_3, C_4, O_1, O_2), electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), respiratory monitoring (nasal thermistor, abdominal and chest strain gauges, and pulse oximetry), and an electromyogram of the anterior tibialis muscle. On the second night of the study only standard recording procedures were used, including EEG (C_3, C_4, O_1, O_2), EOG, and submental EMG. As the recordings obtained the first night were considered adaptation recordings, only data acquired on the second night were analyzed.

Trained raters blinded to the diagnosis of patients visually scored the recordings using a 30-s epoch, according to the criteria of Rechtschaffen and Kales (1968). The sleep variables evaluated were divided into 3 groups: sleep continuity (sleep efficiency, total sleep time, sleep period time, sleep latency, and number of awakenings), sleep architecture (the percentages of sleep stages 1, 2, 3, and 4, and REM sleep), and REM measures (REM latency and REM density).

Sleep efficiency (SE) was defined as the percentage of time spent asleep divided by the total recording period. Total sleep time (TST) was defined as total minutes of sleep obtained during the recording period. Sleep period time (SPT) was defined as the time from the onset of sleep to the final awakening during the recording. Sleep latency (SL) was defined as the time from the beginning of the recording period to the onset of stage 2 sleep that contininued for at least 10 uninterrupted minutes of stage 2, 3, or 4 sleep. The number of awakenings (NA) was defined as the number of awakenings with at least 1 epoch of the awakening stage during the sleep period time. The percentages of stage 1, 2, 3, and 4, and REM sleep were defined as the ratio of the time spent in each stage: the sleep period time. REM latency was defined as the time between sleep onset and the first 3 min of REM sleep minus the time awake during the interval. Rapid eye movements were determined using visual scoring based on the criteria of excursions of at least 25 µvolts within 200 ms (Benson and Zarcone 1993). The REM densities were calculated by dividing the number of eye movements by the minutes of REM sleep.

Statistical analysis

Non-parametric analysis was used due to the small sample size and large standard deviations for many of the variables. The significance of differences between groups was assessed using the Mann-Whitney U test. Non-parametric

Spearman's Rho coefficients (two tailed) were used to test the relationships between the sleep variables and clinical measures. P values ≤ 0.05 were considered significant.

RESULTS

The sleep variables for second-night polysomnography in the schizophrenia patients and controls are presented in Table 1. The schizophrenia patients had significantly impaired sleep continuity, as compared to the controls. The patient group had less total sleep time (P = 0.002), lower sleep efficiency (P < 0.001), longer sleep latency (P = 0.026), more awakenings (P = 0.006), and longer duration of awakenings after falling asleep (P < 0.001) than did the control group. With regard to sleep architecture, no significant differences were observed in the percentages of stage 1, 2, 3, or 4 sleep measures between the groups; however, the percentage of REM sleep in the patients group was less than that in the control group. Significant differences were not observed in REM sleep latency or REM density between the patient and control groups.

Significant differences in sleep variables between the drug-naive patients (n = 6) and those previously treated (currently drug free) (n = 7) were not observed, except for sleep period time (z = — 2.14, P = 0.035). the drug-naive schizophrenia patients had significantly lower sleep efficiency (z = — 2.58, P = 0.008), longer duration of awakenings (z = — 2.15, P = 0.035) and less REM sleep (z = — 2.38, P = 0.014) than the control group. The drug-free patients had significantly lower sleep efficiency (z = — 2.75, P = 0.004), less total sleep time (z = — 2.49, P = 0.011), longer duration of awakenings (z = — 2.69, P = 0.004) and less REM sleep (z = — 2.83, P = 0.002) than the controls. There weren't any statistical differences in symptom severity scores (BPRS, SANS and SAPS total scores) between the drug-naive and drug-free schizophrenia patients (Table 2).

Correlation analysis between the severity of clinical symptoms and sleep variables showed that there was a positive correlation between BPRS score and the percentage of stage 2 sleep (r = 0.630, P = 0.021) and an inverse correlation between SANS score and REM latency (r = — 0.722, P = 0.005). Formal thought disorders were inversely correlated with the percentage of slow-wave sleep (r = — 0.699, P = 0.011) and the sleep variables were not correlated with illness duration (Table 3).

DISCUSSION

The results of the present study show that the patients that were drug-free patients for a minimum 2 months and the drug-naive patients had sleep continuity disturbances (lower sleep efficiency, less total sleep time, longer sleep latency, and more awakenings) and less REM sleep. There was no difference in slow-wave sleep between the patient and normal control groups.

TABLE 1. Comparison of mean sleep variable values between the patient and control groups.

	Schizophrenia Group (n = 13)	Control Group (n = 13)		
Sleep Variables	Mean ± SD	Mean ± SD	z	P
Age (years)	24.4 ± 5.9	25.3 ± 5.0	— 0.61	0.599
Duration of diseases (months)	55.4 ± 62.6	…	…	…
BPRS	32.2 ± 6.6	…	…	…
SANS	44.4 ± 20.9	…	…	…
SAPS	29.8 ± 18.3	…	…	…
Total sleep time (min)	324.4 ± 59.9	404.9 ± 51.7	— 2.98	0.002*
Sleep period time (min)	378.7 ± 48.7	400.7 ± 49.9	— 1.30	0.277
Sleep efficiency (%)	78.3 ± 16.0	95.2 ± 1.8	— 3.75	0.001*
Number of awakenings	21.1 ± 8.3	12.6 ± 4.7	— 2.67	0.006*
Duration of awakenings (min)	54.3 ± 51.7	9.3 ± 3.7	— 3.48	0.001*
Sleep latency (min)	59.1 ± 74.3	12.1 ± 9.8	— 2.23	0.026*
Stage 1 (%)	2.4 ± 1.5	2.4 ± 1.4	— 0.03	0.910
Stage 2 (%)	67.8 ± 10.6	59.6 ± 6.2	— 1.80	0.072
Stage 3 (%)	6.6 ± 2.4	6.9 ± 1.7	— 0.23	0.820
Stage 4 (%)	10.8 ± 10.4	13.2 ± 5.3	— 0.90	0.392
Stage 3-4 (%)	17.4 ± 10.4	20.3 ± 6.2	— 0.81	0.424
REM sleep (%)	12.1 ± 3.9	17.5 ± 2.5	— 3.18	0.001*
REM latency (min)	93.0 ± 47.7	103.5 ± 37.1	— 0.89	0.392
REM density	5.9 ± 3.4	5.3 ± 1.8	— 0.14	0.910

BPRS: Brief Psychiatric Rating Scale; SANS: Scale for Assessment of Negative Symptoms; SAPS: Scale for Assessment of Positive Symptoms; SD: standard deviation. *P ≤ 0.05.

TABLE 2. Comparison of sleep variables between the drug-naive/drug-free patients and controls.

	Drug-naive Schizophrenia Group (n = 6) A	Drug-free Schizophrenia Group (n = 7) B	Normal Control Group (n = 7) C	Pairwise comparison
Sleep Variables	Mean ± SD	Mean ± SD	Mean ± SD	P
Age (years)	24.0 ± 4.4	24.8 ± 7.3	24.2 ± 4.6	…
Duration of diseases (months)	25.1 ± 28.1	81.4 ± 73.9	…	…
BPRS	35.5 ± 5.6	29.4 ± 6.4	…	…
SANS	34.6 ± 15.9	52.8 ± 22.1	…	…
SAPS	39.8 ± 18.1	21.3 ± 14.5	…	…
Total sleep time (min)	350.5 ± 29.4	302.1 ± 72.1	399.9 ± 62.3	B < C
Sleep period time (min)	410.8 ± 41.3	351.3 ± 37.6	388.8 ± 56.0	A > B
Sleep efficiency (%)	83.3 ± 11.4	74.0 ± 18.9	95.0 ± 2.1	A < C, B < C
Number of awakenings	21.6 ± 5.9	20.6 ± 10.4	14.3 ± 5.0	…
Duration of awakenings (min)	60.3 ± 58.4	49.2 ± 49.5	10.3 ± 3.7	A > C, B > C
Sleep latency (min)	28.2± 21.7	85.6 ± 94.3	14.2 ± 10.7	…
Stage 1 (%)	3.1 ± 2.0	1.8 ± 0.7	2.4 ± 1.1	…
Stage 2 (%)	70.2 ± 12.5	65.8 ± 9.3	59.8 ± 7.5	…
Stage 3 (%)	6.1 ± 1.4	7.0 ± 3.1	6.1 ± 1.4	…
Stage 4 (%)	8.6 ± 10.9	12.7 ± 10.6	13.3 ± 5.4	…
Stage 3-4 (%)	14.8 ± 9.7	19.7 ± 11.2	19.7 ± 6.4	…
REM sleep (%)	11.8 ± 4.8	12.3 ± 3.5	18.0 ± 2.5	A < C, B < C
REM latency (min)	102.2 ± 52.6	85.1 ± 45.8	101.1 ± 34.4	…
REM density	6.1 ± 2.2	5.7 ± 4.4	5.3 ± 2.2	…

BPRS: Brief Psychiatric Rating Scale; SANS: Scale for Assessment of Negative Symptoms; SAPS: Scale for Assessment of Positive Symptoms; SD; standard deviation. *P ≤ 0.05.

TABLE 3. Correlation between the sleep variables and clinical symptoms in the patient groups.

Sleep Variables	Delusion	Hallucination	Attention	Formal Thought Disorder	SANS	SAPS	BPRS	Duration of Disease
	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Number of awakenings	0.124 (0.702)	-0.096 (0.766)	0.252 (0.430)	-0.068 (0.835)	0.177 (0.562)	0.161 (0.600)	0.122 (0.692)	-0.330 (0.271)
Duration of awakenings	-0.530 (0.076)	-0.103 (0.751)	0.410 (0.185)	-0.417 (0.177)	0.355 (0.234)	-0.371 (0.212)	-0.533 (0.061)	-0.205 (0.501)
Stage 1 (SPT, %)	-0.089 (0.783)	0.112 (0.730)	0.279 (0.380)	-0.132 (0.683)	0.234 (0.442)	-0.050 (0.871)	-0.312 (0.299)	-0.354 (0.235)
Stage 2 (SPT, %)	0.543 (0.068)	0.062 (0.848)	-0.372 0.234	0.694* (0.012)	-0.383 (0.197)	0.413 (0.160)	0.630* (0.021)	0.131 (0.671)
Stage 3 + 4 (SPT, %)	-0.225 (0.481)	-0.030 (0.926)	0.390 (0.210)	-0.699* (0.011)	0.264 (0.383)	-0.229 (0.452)	-0.523 (0.067)	-0.164 (0.593)
REM Sleep (SPT, %)	-0.124 (0.701)	0.120 (0.711)	0.067 (0.836)	0.159 (0.622)	0.139 (0.652)	-0.003 (0.993)	0.268 (0.375)	0.228 (0.454)
REM latency	0.397 (0.201)	0.151 (0.640)	-0.350 (0.264)	0.497 (0.100)	-.0722* (0.005)	0.426 (0.147)	0.102 (0.741)	0.324 (0.281)
REM Density	-0.386 (0.215)	-0.333 (0.291)	0.277 (0.383)	-0.163 (0.614)	0.176 (0.565)	-0.127 (0.680)	-0.099 (0.748)	0.022 (0.943)

BPRS: Brief Psychiatric Rating Scale; SANS: Scale for Assessment of Negative Symptoms; SAPS: Scale for Assessment of Positive Symptoms; SD; standard deviation; SPT: Sleep Period Time.
*P ≤ 0.05.

The results of the present study, including lower sleep efficiency, less total sleep time, longer sleep latency, and more awakenings among schizophrenia patients are consistent with most of the puplished results of sleep studies on schizophrenia (Jus et al. 1973; Ganguli et al. 1987; Kempenaers et al. 1988; Benson et al. 1991, 1996; Van Cauter et al. 1991; Tandon et al. 1992; Benson and Zarcone 1993; Hudson et al. 1993; Lauer et al. 1997; Keshavan et al. 1998; Nishino et al. 1998; Poulin et al. 2003; Yang and Winkelman 2006). Sleep continuity disturbances are also frequently observed in other psychiatric disorders and neurological disorders. As such, they are not regarded as alterations specific to schizophrenia; however, it has been proposed that the presumed over-activity of the dopaminergic system in schizophrenia and the involvement other neurotransmitter systems, such as the GABAergic system, may play a role in disturbances in sleep initiation and maintenance.

In the present study schizophrenia patients had less total REM sleep than the controls. The number of sleep studies on the effects of dopaminergic over-activity, which is the presumed essential neurochemical pathology in schizophrenia, on REM sleep is limited. In experimental studies the dopamine D_2 agonists apomorphine, pergolide, and bromocriptine were shown to enhance wakefulness and reduce REM sleep (Monti et al. 1988; Stenberg and Porka-Heiskanen 1990). These studies showed that reduced REM sleep in schizophrenia might be explained by increased D2 receptor activity.

In the present study REM latency did not differ between the patient and control groups, as was reported in other studies (Gaillard et al. 1984; Ganguli et al. 1987; Lauer et al. 1997; Keshavan et al. 1998; Hoffmann et al. 2000; Sekimoto et al. 2006; Yang and Winkelman 2006). Some studies reported that schizophrenia patients have shortened REM latency (Jus et al. 1973; Benson et al. 1991, 1993; Tandon et al. 1992; Hudson et al. 1993; Röschke et al. 1998; Poulin et al. 2003); however, shortened REM latency in schizophrenia has not been interpreted in the light of the data available from structural, neurochemical, and neuroendocrine studies (Chouinard et al. 2004). As such, alteration in REM latency is not considered specific to schizophrenia.

REM density in the present study did not differ between the schizophrenia patients and controls, as was previously reported (Ganguli et al. 1987; Lauer et al. 1997; Keshavan et al. 1998; Poulin et al. 2003; Yang and Winkelman 2006). It has been proposed that alterations in REM density might be associated with the disturbance of sleep continuity and night-by-night differences in the sleep architecture (Riemann et al. 1994); however, although sleep continuity was impaired in the schizophrenia patients in the present study, REM density did not differ between the patients and controls.

In the present study total slow-wave sleep in the schizophrenic patients and controls did not differ. This result is consistent with that of other studies (Ganguli et al. 1987; Kempenaers et al. 1988; Tandon et al. 1992; Hudson et al. 1993; Lauer et al. 1997; Keshavan et al. 1998; Poulin et al. 2003); however, some studies reported less slow-wave sleep (Benson et al. 1991, 1996; Benson and Zarcone 1993; Sekimoto et al. 2006; Yang and Winkelman 2006) and it has been proposed that reduced slow-wave sleep may be a typical and pathognomonic sleep alteration in schizophrenia. Additionally, it has been known that slow-wave sleep is affected in some chronic neurodegenerative disorders. Along with schizophrenia being a long-term disorder, it is possible that some of its features, such as chronicity, the residual effects of the drugs, or symptomatology, might affect slow-wave sleep. A meta-analysis of sleep in schizophrenia indicated that disturbances in slow-wave sleep might be related to the duration of illness and symptomatology (Chouinard et al. 2004).

The effects of neuroleptics and anticholinergic drugs on sleep structure and especially REM sleep are unclear. The effects of neuroleptics on sleep could vary, depending on the molecular structure, dose, and the duration of drug use (short-term vs. long-term (Neylan et al. 1992). Positron emission tomographic scanning studies report that neuroleptic binding to dopamine receptors disappears from the brain within 2 weeks of neuroleptic withdrawal (Campbell and Baldessarini 1985; Tamminga et al. 1988). Furthermore, according to some studies, a single dose of haloperidol can have an antidopaminergic effect, even after 40 days (Antelman et al. 1986; van Sweden 1987), and that metabolites of neuroleptics may still be detectable in patients several months after neuroleptic withdrawal (Campbell et al. 1985). As such, the long-term effects of neuroleptics on sleep should not to be excluded in sleep studies on schizophrenia.

In consideration of the above-mentioned data, the present study included previously medicated schizophrenia patients that were drug-free for at least 2 months and drug-naive schizophrenia patients. When both schizophrenia patient subgroups were compared with the control group the patients exhibited sleep continuity disturbances and reduced REM sleep (Table 2). Similar findings in both patient subgroups indicate that sleep continuity disturbances and reduced REM sleep may be characteristic of schizophrenia.

Correlation analysis between the clinical findings and sleep variables showed that the severity of negative symptoms was negatively correlated with REM latency. This finding is consistent with previous reports (Thaker et al. 1990; Taylor et al.1991; Tandon et al. 1992). In addition, some studies reported a correlation between REM latency, and the severity of global symptoms and positive symptoms (Taylor et al.1991; Tandon et al. 1992; Lauer et al. 1997); however, although short REM latency is associated with depressive symptomatology, the clinical significance of REM sleep abnormalities in schizophrenia remains unclear.

Some studies reported an association between reduced slow-wave sleep and the severity of negative symptoms (Ganguli et al. 1987; Tandon et al. 1989; Keshevan et al. 1995; Yang and Winkelman 2006). It has also been proposed that reduced slow-wave sleep has a a association with formal thought disorder or cognitive dysfunction, which might indicate frontal cortex dysfunction (Yang and Winkelman 2006). In the present study, a relationship between negative symptoms total score and slow-wave sleep was not observed: yet, a negative correlation was observed between formal thought disorders and reduced slow-wave sleep. This finding might indicate that there is frontal cortex dysfunction in schizophrenia. The frontal cortex appears to play an important role in the generation of slow-wave sleep activity and it is thought that slow-wave sleep may play a critical role in memory consolidation (Gais and Born 2004). Although correlational studies on sleep abnormalities reported a relationship between reduced slow-wave sleep and cognitive dysfunction, these results were based on symptom severity scales, such as BPRS, SANS, and SAPS; therefore, additional research based on comprehensive neuropsychological tests are necessary in order to obtain more conclusive data.

In the present study a relationship between longer stage 2 sleep, and the severity of negative symptoms and formal thought disorders was observed. This finding might be related to increased stage 2 sleep as a consequence of reduced slow-wave sleep. Some studies reported that hallucinations and delusions were associated with reduced REM latency (Tandon et al. 1992; Lauer et al. 1997; Poulin et al. 2003) and increased REM density (Benson and Zarcone 1993); however, a significant relationship between hallucinations and delusions, and sleep variables were not observed in the present study.

To the best of our knowledge the present study is the first polysomnographic study of schizophrenia patients in Turkey; however, there are several limitations. First, the sample size was small. It is obvious that a larger study group would have provided data beter suited to generalizing the findings to the entire population of schizophrenia patients. Second, the study included patients with varying durations of illness, limiting the homogeneity of the patient group. The third limitation is the selection of only patient with the undifferentiated subtype of schizophrenia. Actually, we aimed to include a homogeneous patient group; however, although there are no available data concerning differences in sleep architecture between patients with different subtypes of schizophrenia, investigating only one subtype of schizophrenia limits the generalizability of the findings to the entire population of schizophrenia patients. The fourth limitation factor is the exclusion of patients with a reported history of alcohol and substance abuse. The fact that we did not perform toxicological investigations could be considered as a limitation.

In conclusion, the present study show that there were disturbances in sleep initiation and maintenance in a group of non-medicated adult male inpatients with schizophrenia, undifferentiated type. With regard to sleep architecture, there were no observed changes in slow-wave sleep, but REM sleep was reduced. This study also shows that there was a relationship between formal thought disorder and reduced slow-wave sleep. Sleep studies in schizophrenia can help us to understand the underlying neurobiology of the illness; however, the relationship between sleep and schizophrenia remains unclear because of the heterogeneous nature of schizophrenia. As such, a schizophrenia-specific sleep pattern has not been identified in sleep studies that included heterogeneous patient samples that might have experienced profound long- or short-term effects of drugs. Studies that include drug-free and/or drug-naive patients with different subtypes of schizophrenia are expected to provide more reliable results.

REFERENCES

Amerikan Psikiyatri Birliği (1994) Mental Bozuklukların Tanısal ve Sayımsal El Kitabı, Dördüncü Baskı (DSM-IV-TR (Çev.ed.:E Köroğlu) Hekimler Yayın Birliği, Ankara.

Andreasen NC (1983) The Scale for the Assessment of Negative Symptoms (SANS) Iowa City, University of Iowa.

Andreasen NC (1984) The Scale for the Assessment of Positive Symptoms (SAPS) Iowa City, University of Iowa.

Antelman SM, Kocan D, Edwards DJ et al. (1986) Behavioral effects of single neuroleptic treatment grow with the passage of time. Brain Res 385: 58-67.

Benca RM, Obermeyer WH, Thisted RA et al. (1992) Sleep and Psychiatric Disorders, A meta-analysis. Arch Gen Psychiatry 49: 651-668.

Benson KL, Faull KL, Zarcone VP (1991) Evidence for the role of serotonin in the regulation of slow wave sleep in schizophrenia. Sleep 14: 133-139.

Benson KL, Sullivan EV, Lim KO et al. (1996) Slow wave sleep and computed tomographic measures of brain morphology in schizophrenia. Psychiatry Res 60: 125-134.

Benson KL, Zarcone VP (1993) Rapid eye movement sleep eye movements in schizophrenia and depression. Arch Gen Psychiatry 50: 474-482.

Campbell A, Baldessarini RJ (1985) Prolonged pharmacologic activity of neuroleptics. Arch Gen Psychiatry 42: 637.

Campbell A, Baldessarini RJ, Teicher MH et al. (1985) Prolonged antidopaminergic actions of single doses of butyrophenones in the rat. Psychopharmacology 87: 161-166.

Chouinard S, Poulin J, Stip E et al. (2004) Sleep in untreated patients with schizophrenia: a meta-analysis. Schizophr Bul 30: 957-967.

Çorapçıoğlu A, Aydemir A, Yıldız M et al. (1999) DSM-IV Eksen I Bozuklukları için Yapılandırılmış Klinik Görüşme. Hekimler Yayın Birliği.

Driver HS (2006) Patterns of Sleep in Women: An Overview. Sleep: A Comprehensive Handbook. Lee-Chiong, Teofilo (ed), Hoboken, New Jersey. John Wiley & Sons Inc, s. 623-627.

Erkoç Ş, Arkonaç O, Ataklı C et al. (1991a) Negatif Semptomları Değerlendirme Ölçeğinin (SANS) güvenilirliği ve geçerliliği. Düşünen Adam 4: 14-19.

Erkoç Ş, Arkonaç O, Ataklı C et al. (1991b) Pozitif Semptomları Değerlendirme

Ölçeğinin (SANS) güvenilirliği ve geçerliliği. Düşünen Adam 4: 20-24.

Feinberg I, Koresko RL, Gottlieb F (1965) Further observations on electrophysiological sleep patterns in schizophrenia. Compr Psychiatry 6: 21-24.

First MB, Spitzer RL, Gibbon M et al. (1997) Structured clinical interview for DSM-IV Axis I Disorders (SCID-I). Clinical version. American Psychiatric Press, Washington DC and London.

Gaillard JM, Iorio G, Campajola P et al. (1984) Temporal organization of sleep in schizophrenics and patients with obsessive compulsive disorder. Adv Biol Psychiat 15; 76-83.

Gais S, Born J (2004) Declarative memory consolidation: mechanisms acting during human sleep. Learn Mem 11: 679-685.

Ganguli R, Reynolds CF, Kupfer DJ (1987) Electroencephalographic sleep in young, never-medicated schizophrenics. A comparison with delusional and nondelusional depressives and with healthy controls. Arch Gen Psychiatry 44: 36-44.

Haffmans PM, Hoencamp E, Knegtering HJ et al. (1994) Sleep disturbance in schizophrenia. Br J Psychiatry 165: 697-698.

Hoffmann R, Hendrickse W, Rush AJ et al. (2000) Slow-wave activity during non-REM sleep in men with schizophrenia and major depressive disorders. Psychiatry Res 95: 215-225.

Hudson JI, Lipinski JF, Keck Jr PE et al. (1993) Polysomnographic characteristics of schizophrenia in comparison with mania and depression. Biol Psychiatry 34: 191-193.

Jus K, Bouchard M, Jus AK et al. (1973) Sleep EEG studies in untreated, long-term schizophrenic patients. Arch Gen Psychiatry 29: 386-390.

Kempenaers C, Kerkhofs M, Linkowski P et al. (1988) Sleep EEG variables in young schizophrenic and depressive patients. Biol Psychiatry 24: 828-833.

Keshavan MS, Reynolds CF, Mievald JM et al. (1998) Delta sleep deficits in schizophrenia. Arch Gen Psychiatry 55: 443-448.

Krystal AD (2006) Sleep and Psychiatric Disorders: Future Direction. Psychiatr Clin N Am 29: 1115-1130.

Lauer CJ, Schreiber W, Pollmächer T et al. (1997) Sleep in schizophrenia: A polysomnographic study on drug-naive patients. Neuropsychopharmacology 16: 51-60.

Monti JM, Hawkins M, Jantos H et al. (1988) Biphasic effects of dopamine D-2 receptor agonists on sleep and wakefulness in the rat. Psychopharmacology 95: 395-400.

Monti JM, Monti D (2004) Sleep in schizophrenia patients and the effects of antipsychotic drugs. Sleep Med Rev 8: 133-148.

Monti JM, Monti D (2005) Sleep disturbance in schizophrenia. Int Rev Psychiatr 17: 247-253.

Neylan TC, van Kammen DP, Kelley ME et al. (1992) Sleep in schizophrenic patients on and of haloperidol therapy. Arc Gen Psychiatry 49: 643-649.

Nishino S, Mignot E, Benson KL et al. (1998) Cerebrospinal fluid prostaglandins and corticotropin releasing factor in schizophrenics and controls: relationship to sleep architecture. Psychiatry Res 78: 141-150.

Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Reports 10: 799-812.

Poulin J, Daoust AM, Forest G et al. (2003) Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. Schizophr Res 62: 147-153.

Rechtschaffen A, Kales A (1968) A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington DC: US Government Printing Office.

Röschke J, Wagner P, Mann K et al. (1998) An analysis of the brain's transfer properties in schizophrenia: amplitude frequency characteristics and evoked potentials during sleep. Biol Psychiatry 43: 503-510.

Sekimoto M, Kato M, Watanabe T et al. (2006) Reduced frontal asymmetry of delta waves during all-night sleep in schizophrenia. Schizophr Bull 16: 1-5.

Soykan C (1989) Institutional differences and case typicality as related to diagnosis system severity, prognosis and treatment. Master Tezi, Ortadoğu Teknik Üniversitesi, Ankara.

Stenberg D, Porka-Heiskanen T (1990) REM sleep need and regulation. Endogenous sleep factors. S Inoue and JM Krueger (ed), Den Haag. SPA Academic Publishing, s.145-154.

Thaker GK, Wagman AMI, Tamminga CA (1990) Sleep polygraphy in schizophrenia: methodological issues. Biol Psychiatry 28: 240-246.

Tamminga CA, Burrows GH, Chase TN et al. (1988) Dopamine neuronal tracts in schizophrenia: their pharmacology and in vivo glucose metabolism. Ann NY Acad Sci 537: 443-450.

Tandon R, Shipley JE, Taylor S et al. (1992) Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. Arch Gen Psychiatry 49: 185-194.

Taylor SF, Tandon R, Shipley JE et al. (1991) Sleep onset REM periods in schizophrenic patients. Biol Psychiatry 30: 205-209.

Van Cauter E, Linkowski P, Kerkhofs M et al. (1991) Circadian and sleep-related endocrine rhythms in schizophrenia. Arch Gen Psychiatry 48: 348-356.

van Sweden B (1987) Rebound insomnia in neuroleptic drug withdrawal: neurophysiological characteristics. Pharmacopsychiatry 20: 116-119.

van Sweden B (1987) REM-latency in neuroleptic drug withdrawal. Acta Psychiatr Belg 84: 235-239.

Yang C, Winkelman JV (2006) Clinical significance of sleep EEG abnormalities in chronic schizophrenia. Schizophr Res 82: 251-260.