https://doi.org/10.5664/jcsm.8776

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Sleep, sleep spindles, and cognitive functions in drug-naive patients with first-episode psychosis

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Study Objectives: Various lines of clinical findings have suggested abnormalities in macro- or microstructural parameters of sleep in patients with schizophrenia. Meanwhile findings are inconclusive due to some confounding factors, such as the heterogeneity of the disorder, drug regimen, and duration of the illness. There are a few studies in the literature that have been conducted on drug-free patients with first-episode psychosis (FEP). Based on this knowledge, we aimed to explore sleep characteristics, sleep spindles, and neuropsychological profiles of the drug-naive patients with FEP.

Methods: The study sample consisted of 21 drug-naive patients with FEP and 21 healthy participants. Polysomnography recordings were conducted for 2 subsequent nights. A neuropsychological test battery was administered for assessing cognitive functions. The Positive and Negative Syndrome Scale was applied to measure symptom severity of the patients. Spindle detection was performed visually.

Results: According to the results of the study, the patient group's percentage of stage N2 sleep and sleep efficiency index was lower than in the control group. Among sleep spindle parameters, spindle density was found to be reduced in the patient group. The results of neuropsychological tests measuring executive functions, learning, and memory support the idea that there is a global cognitive deterioration from the early course of the disorder. In the psychotic group, negative symptoms were negatively correlated with verbal memory, learning, verbal fluency, and semantic organization. We found that the percentage of stage N3 sleep decreased while negative symptom severity increased. In addition, the percentage of stage N1 sleep increased as negative symptom severity increased. Reduction in stage N3 sleep was associated with an impairment in learning, verbal fluency, and response inhibition. The sleep spindle density and cognitive functions did not show any associations.

Conclusions: Taken together, these findings suggest that patients with FEP show global cognitive impairment (except for attention and processing speed), which is associated with changes in sleep architecture and higher score in a scale assessing negative symptoms. We conclude that cognitive function and spindle parameters differ nonlinearly among patients with FEP.

Keywords: first-episode psychosis, sleep, sleep architecture, sleep spindle, neuropsychology, schizophrenia

Citation: Yazıhan NT, Yetkin S. Sleep, sleep spindles, and cognitive functions in drug-naive patients with first-episode psychosis. *J Clin Sleep Med*. 2020;16(12):2079–2087.

BRIEF SUMMARY

Current Knowledge/Study Rationale: There have been few studies in the literature exploring sleep, sleep spindles, and cognitive functioning of drug-naive patients with first-episode psychosis (FEP).

Study Impact: We found a decrease in the percentage of stage N2 sleep and sleep efficiency index in the FEP group compared with the healthy control group. Moreover, the density of sleep spindles was found to be reduced in FEP. Patients with FEP showed impairments in learning, memory, cognitive flexibility, verbal fluency, response inhibition, and working memory and these deficits were associated with the changes in sleep architecture and severity of the negative symptoms. The percentage of stage N3 sleep was negatively correlated with negative symptom severity. On the contrary, the amount of stage N1 sleep was positively correlated with negative symptoms. We did not find any associations between sleep spindle density and any of the cognitive domains. We conclude that cognitive function and spindle parameters differ nonlinearly among patients with FEP.

INTRODUCTION

Sleep disturbances and cognitive dysfunction are extremely common in patients with psychotic disorders and are cardinal features of schizophrenia.[1–5] Polysomnography studies conducted in patients with schizophrenia revealed that total sleep time of patients was reduced,[6–8] sleep efficiency was decreased,[8–13] and sleep latency was increased.[13–20] In addition, total awake time was found to be longer in patients with schizophrenia.[13,19–21]

However, schizophrenia studies on different stages of sleep are still inconsistent. While some studies found that the duration and percentage of stage N2 sleep was increased,[8,19,21,22] others reported no such changes.[11,18] The duration and percentage of slow-wave sleep in the third and fourth stages (according to the previous classification system) were generally found to be reduced. Slow-wave sleep was shown to decrease in most studies.[18–26] In research on rapid eye movement (REM) latency, conflicting results have been obtained, with some studies reporting a decrease[6,21,26–30] and others suggesting no change.[8,20,31,32] Similarly, some studies reported no change in the percentage of REM sleep,[6,7,23,28,32] whereas others found a significant decrease.[13,18,21,30,31]

The inconsistent results obtained from the literature have been attributed to the heterogeneity of the sample and treatment

protocol. However, some researchers have claimed that sleep changes presented independently from treatment and mood effects.[21] Moreover, few studies have compared never-medicated young patients with schizophrenia to healthy control group with respect to sleep. Research conducted in nonmedicated acute patients and drug-naive patients found an increase in sleep latency and awake time, and a decrease in total sleep time and sleep efficiency in both populations.[6,13,18,33,34] In short, studies conducted in nonmedicated patients with first-episode schizophrenia reported difficulties in initiating and maintaining sleep.[29]

Sleep spindles, which are one of the microstructural graph elements of electroencephalography (EEG), have attracted steadily increasing attention in recent years. Sleep spindles are phasic bursts of thalamocortical activity and typically defined as 11–16 Hz (in the sigma frequency band) with a duration of between 0.5 and 2 seconds. They are most prominent during stage N2 sleep and one of the defining features of this stage. Functionally, sleep spindles are involved in the processes of offline memory consolidation and stabilization of the sleep by inhibiting perception of external stimuli.[35–37] In addition, sleep spindles facilitate neuroplasticity, which refers to the brain's ability to reorganize and generate new neuronal pathways in response to internal and external stimuli.[38] Several lines of evidence implicate dysfunctional neuronal plasticity in the pathophysiology of schizophrenia. According to the available literature, sleep spindle density was found to be reduced in patients with schizophrenia, and the reduction in the spindle activity was found to correlate with a reduction in encoding ability.[34,39–41] The accumulating evidence on sleep spindle deficits in schizophrenia suggests that it might be a biological indicator of the disorder. Sleep spindle abnormalities have been associated with the pathophysiology of schizophrenia through thalamic abnormalities.[42]

Another subject we wanted to investigate was the cognitive functioning of patients with first-episode psychosis (FEP). Neurocognitive impairments have long been known to be one of the core symptoms of schizophrenia.[43–46] Studies comparing patients with healthy individuals have revealed cognitive deficits regarding different brain functions.[47] Moreover, studies have found that cognitive impairment exists in the prodromal phase and persists into the acute stages of the disorder.[44] Mild cognitive impairment has been found among high-risk individuals[48,49] and relatives without any history of schizophrenia.[50,51] A meta-analysis that focused on findings from the first-episode drug-naive patients (from 1992 to 2013) reported a broad range of impairment in all neurocognitive areas from moderate to severe levels, with the most impaired domains being verbal memory, information-processing speed, and working memory.[52]

A large number of studies have shown that sleep problems are associated with poorer cognitive functioning. A reduction in slow-wave, theta, and sigma activities, and abnormalities in spindle characteristics during non-REM sleep were found to be associated with a greater risk of occurrence of cognitive impairment.[34,39,41,53] Sleep disorders occur at a high rate in early nonaffective psychosis, which were found to be associated with symptom severity.[54] In addition, alterations in sleep were correlated to the severity of psychotic and cognitive symptoms, and episodes of insomnia were related to the exacerbation of psychotic symptoms.[55,56] Studies suggest that sleep disturbances are related to the severity of the illness, level of distress experienced by the patient and his/her family, and reduction in the quality of life.[57,58] Therefore, studies have explored sleep and cognitive parameters in order to formulate hypotheses about the pathophysiology of schizophrenia.[59]

Considering these findings, the main aim of this study was to investigate sleep architecture, sleep spindles, and sleep maintenance in first-episode drug-naive patients and to determine the characteristics of cognitive functioning. Based on earlier findings, we hypothesized that, compared with controls, sleep maintenance difficulties would increase and spindle density would decrease in the FEP group. Neuropsychological test scores measuring attention-psychomotor speed, memory-learning, and executive functions were expected to be reduced in the FEP group when compared with the control group. The examination of change in sleep architecture was exploratory. The investigation of possible correlations between the Positive and Negative Syndrome Scale (PANSS), sleep parameters, and neuropsychological tests was also exploratory.

METHODS

Participants

The study sample consisted of 25 drug-naive male inpatients with FEP hospitalized at Gülhane Research and Training Hospital, Ankara (formerly Gülhane Military Medical Academy) and 27 healthy volunteers with similar sociodemographic characteristics. The study was conducted between May 2015 and November 2016. In the current study, convenience sampling was used. The healthy volunteer participants were recruited through announcements that contained brief information about the nature of study and enrollment instructions.

Using polysomnography, the whole-night sleep records of the participants were obtained on 2 consecutive nights. Because of reasons such as adaptation difficulties to the laboratory environment or having a diagnosis of schizoaffective disorder, 4 patients were excluded from the study. According to the healthy participants' data, reasons for exclusion included short sleep duration (n = 2, <250 minutes), detection of sleep apneas that might cause sleep fragmentation (n = 3, >5 events/h), and sleep efficiency index lower than 84% (n = 1). The healthy group had no medical or psychological conditions and did not take any medications that might affect their sleep pattern and neuropsychological measures. All of the healthy participants reported regular sleep–wake schedules, and their sleep efficiency index rates were higher than 84%.

The participants were informed that alcoholic and caffeinated beverages should not be consumed on the day of sleep recording and the night before. One of the inclusion criteria for both groups was completing 8 years of education. Ultimately, the second night's sleep recordings for 21 drug-naive patients with FEP and 21 healthy participants were included for further statistical analysis.

Neuropsychological assessment

A neuropsychological test battery comprising the Stroop test Temel Bilimler Arastirma Grubu (TBAG), Trail Making Test A and B, Controlled Oral Word Association Test, Serial Digit Learning Test, and the Auditory Verbal Learning Test was administered after 5:00 PM, before the second night of sleeping session. Neuropsychological tests were administered in 3 sessions by the same trained examiner and lasted approximately 90 minutes. The first session included the Stroop test TBAG version (SP) and Trail Making Test A and B. The second session included the Serial Digit Learning Test and Controlled Oral Word Association Test. The third session included the Auditory Verbal Learning Test and Wechsler Adult Intelligence Test–Coding. The sessions and, where there was more than 1 test, the order of the tests within each session were counterbalanced and the participants received a 10-minute break between each session.

Stroop test TBAG version

Stroop test measures processing speed, focused attention, selective attention, and resistance to interference. The test requires reading color names, naming colors correctly, and inhibiting a competing automatic response.[60,61]

Controlled Oral Word Association Test

The test measures verbal fluency, cognitive flexibility, and semantic organization. It uses the 3-letter set of K, A, and S to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with 1 of these letters. The procedure is then repeated for the remaining 2 letters. Finally, the tester gives the category "animal" and wants the individual to produce as many words as possible in that category.[62]

Auditory Verbal Learning Test

This test includes 2 different word lists, each comprising 15 words that are repeated over different trials that the individual is asked to repeat. It evaluates plasticity and a wide diversity of memory function: short-term auditory-verbal memory, encoding, free recall, learning, retroactive and proactive interference, retention of information, and immediate-delayed memory.[63,64]

Serial Digit Learning Test

This test consists of a mixed series of numbers ranging from 1 to 9. The numbers are read in succession and then the test participant is requested to remember and repeat the number set verbally in the correct order. When the participant recalls the digit series correctly the test is terminated.[61,65]

Trail Making Test

The Trail Making Test is a mental flexibility test that gives information about visual-motor scanning, speed of processing, set switching, working memory, and executive functions. The test consists of forms A and B, each containing 25 circles. In form A, which is administered first, participants are directed to follow the numbers 1 to 25 and connect them sequentially by drawing a line. In the other form, circles should be connected in the sequence number-letter (1-A, 2-B, 3-C, etc).[66,67]

Wechsler Adult Intelligence Test–Coding

The coding task, which measures processing sped, requires an individual to copy (with a pencil) the appropriate symbol in a box underneath a digit (1 to 9) using a key at the top of the page containing digits and their corresponding symbols.[68]

PANSS

The PANSS is a semistructured interview scale developed to assess positive and negative symptoms and general psychopathology in schizophrenia or other psychotic disorders and to measure the level of these symptoms.[69]

Procedures

The examination of the inpatients was undertaken by 2 psychiatrists. Those who met the study criteria and whose families gave written consent were included in the study. The prediagnosis of each patient was assessed using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* and PANSS was administered to measure symptom severity. To establish a final diagnosis, the patients' 3- and 6-month follow-up examinations were planned. The medical history and other information that might be related to the disorder were obtained from the patients and their first-degree relatives. To determine whether the patient was in the first psychotic episode, the records of the interviews with the patient and their companions, and hospital, and prescription information system were also examined. These patients were scheduled for sleep recordings and test sessions within 4 days of admission to the clinic.

Our healthy population consisted of hospital staff, the relatives of the staff, and the university students. After we connected with the potential participants we invited them to the sleep laboratory in order to explain the nature of our study, take their written consent, and examine their sleep habits and psychiatric conditions and make sure that they were following a regular sleep–wake schedule Participants were examined by a psychiatrist in terms of their sleep habits and psychiatric symptoms through a semi-structured interview form that lasted approximately 45 minutes.

Neuropsychological tests were performed just before the second night of sleep recording. PANSS was administered to the patients by a psychiatrist during the patients' hospital stay. Participants stayed at the sleep laboratory from 10:30 PM to 07:00 AM for 2 consecutive nights, and recordings were made in individual bedrooms using a digital polygraph. The data were collected using Grass AS40 polysomnography (Comet-Plus PSG, Natus Neurology, Middleton, WI, USA) at a sampling frequency of 200 Hz. Electrodes (F3, F4, C3, C4, O1, O2) were placed according to the International 10–20 system. On the first night of the study, a full-montage polysomnogram was recorded in order to examine primary sleep disturbances, consisting of an EEG, an electro-oculogram, a submental electromyogram, an electrocardiogram, respiratory monitoring (airflow, respiratory effort, oxygen saturation), and an electromyogram of the anterior tibialis muscle. On the second night of the study, recordings included only EEG, electro-oculogram,

and submental electromyogram. The data collected from the second night recording were included in further analysis.

Each 30-second epoch of sleep was scored visually according to the American Academy of Sleep Medicine, version 2.2, rules.[70] The formulas we used to calculate sleep efficiency, sleep percentage, and wake after sleep onset are, respectively: (1) total sleep time (actual sleep time)/time in bed (× 100), (2) sleep % = total period of each sleep stage/total sleep time (actual sleep time) (× 100), and (3) wake after sleep onset = periods of wakefulness occurring after defined sleep onset.

Sleep spindle activity is best viewed over the central regions of the head. To detect spindles, we focused on the left central electrode (C3), and all N2 epochs were scanned visually. Each 30-second epoch was analyzed after being high-pass band filtered at 0.3 Hz and low-pass band filtered at 35 Hz. Spindles were detected and counted by an expert visually using the following steps: (1) detecting and selecting the spindles from the C3-M2 channel, (2) applying fast Fourier transform to each spindle detected, and (3) analyzing the spindle characteristics such as frequency (mean and peak), amplitude, and duration by using the fast Fourier transform algorithm automatically. Since the spindle detection was made visually, we used only 1 of the central channels. Sleep records, which consisted of 16,255 epochs, were visually inspected and the spindle density of each participant was calculated as the mean number of spindles per 30 seconds.

Statistical analysis

To test whether there were significant differences between groups in terms of sleep architecture and maintenance of sleep, multivariate analysis of variance was used. To examine the difference between two groups in terms of attention-processing speed, learning-memory, and executive functions multivariate analysis of covariance was used. The significance of differences of sleep spindle density among groups was assessed by Student' *t* test. Finally, to determine the relationship between sleep parameters, PANSS scores and neuropsychological variables, Pearson's correlation was used.

RESULTS

The mean age of the FEP group was 22.66 (±2.39), and the mean age of the control group was 22.71 ± 3.45 years; the groups did not differ significantly [$t(40) = .052$, $P = .959$]. The mean number of years of education in the psychosis group was 11.23 (±2.71) and that of the control group was 12.57 (±1.91); the groups were not significantly different [$t(40) = 1.838$, $P = .073$]. The mean scores of the PANSS total, positive symptoms, and negative symptoms were 94.50 ± 11.15, 20.65 ± 4.24, and 25.75 ± 5.31, respectively. Among the patients, 5 could not be diagnosed because they did not come to the sixth-month follow-up appointments. The rest of the patients were diagnosed as having schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, criteria. Of 42 participants, 1 patient and 2 healthy controls were excluded before starting sleep spindle detection. Since the spindles were detected visually, any epoch with artifact thought to affect the spindle detection was excluded.

To examine the difference between the study and control group, multivariate analyses of variance were conducted separately for the variables involving sleep maintenance and sleep architecture. Statistically significant multivariate analysis of variance effects were obtained, and differences between the 2 groups in sleep architecture [Wilks' lambda = .700, $F(4,37) = 3.96$, $P = .009$, $\eta^2 = .300$] and sleep maintenance [Wilks' lambda = .720, $F(4,37) = 3.60$, $P = .014$, $\eta^2 = .280$] are presented in **Table 1** and **Table 2**. The statistical significance level was defined as $P < .0125$ after Bonferroni correction. Similarly, the differences between 2 groups in terms of neuropsychological test scores were analyzed separately for attention-processing speed [Wilks' lambda = .606, $F(5,22) = 2.86$, $P = .039$, $\eta^2 = .394$], learning-memory [Wilks' lambda = .257, $F(5,27) = 12.36$, $P = .000$, $\eta^2 = .696$], and executive functions [Wilks' lambda = .457, $F(5,21) = 4.99$, $P = .004$, $\eta^2 = .543$] using multivariate analysis of covariance. The year of education which could potentially affect the participants' performance was added as a covariate in the model (**Table 3**, **Table 4**, and **Table 5**). The statistical significance level was defined as $P < .01$ after Bonferroni correction. Finally, Student's *t* test was performed for sleep spindle density, which is shown in **Table 1** [$t(37) = 2,154$, $P = .038$]. The characteristics of sleep stages and spindle parameters are shown in **Table 6**.

To investigate the relationship between PANSS 1(+) positive, PANSS 2(−) negative symptoms and both sleep and neuropsychological tests, Pearson's correlation coefficients were computed (**Table 7** and **Table 8**).

DISCUSSION

In the current study, sleep efficiency index was lower in individuals with psychosis than in those in the control group. When sleep structure was examined, we found a reduction in the percentage of stage N2 sleep in FEP. We also found a reduction in the density of sleep spindles in FEP when compared with the control group. Results of the neuropsychological assessment showed that a wide range of higher cognitive functions were affected in drug-naive patients with FEP.

A meta-analysis published in 2004 reported an increase in sleep latency and a decrease in total sleep duration and sleep efficiency in patients with schizophrenia.[21] The authors also reported that, among patients who were not taking medication, the awake time was increased and the percentage of second-stage sleep was reduced. According to the results of another meta-analysis study conducted in 2017,[71] nonmedicated patients had shorter total sleep time, longer sleep onset, lower sleep efficiency index score, and longer total awake time than the control group. However, in the current study, the only statistically significant difference between groups was found in sleep efficiency index.

In the literature regarding FEP, there are less consistent findings related to the durations and percentages of slow-wave sleep, second-stage sleep, and REM sleep, as well as REM latency and intensity.[6,7,18,21,72] Although some researchers

Table 1—MANOVA comparisons for sleep architecture and *t* test results for spindle density.

	FEP	Control	*F*	*P*	η^2
Sleep architecture[a] %					
N1	12.82 ± 5.07	10.27 ± 3.19	3.78	.059	.086
N2	46.00 ± 6.48	51.29 ± 5.27	8.43	.006*	.174
N3	19.99 ± 7.63	20.81 ± 4.98	.170	.683	.004
REM	21.16 ± 8.39	17.52 ± 3.81	3.25	.079	.075
Spindle density[b]	0.78 ± 0.32	1.030 ± 0.38	2.145[c]	.038**	—

Values are means ± SDs unless otherwise indicated. *P < .0125, **P < .05. FEP = first-episode psychosis; MANOVA = multivariate analysis of variance; N = non–rapid eye movement; REM = rapid eye movement. [a]FEP, n = 21; Control, n = 21. [b]Spindle density: FEP, n = 21; Control, n = 19. [c]*t* Test.

Table 2—MANOVA comparisons of groups in terms of sleep maintenance.

	FEP (n = 21)	Control (n = 21)	*F*	*P*	η^2
Sleep latency, minutes	26.12 ± 19.50	14.48 ± 8.71	6.24	.017	.135
WASO, minutes	41.09 ± 39.37	30.19 ± 20.11	1.12	.26	.031
TST, minutes	388.51 ± 54.13	408.43 ± 26.56	2.29	.138	.054
SEI, %	84.32 ± 9.95	90.66 ± 4.63	6.98	.012*	.149

Values are means ± SDs unless otherwise indicated. *P < .0125. FEP = first-episode psychosis; MANOVA = multivariate analysis of variance; REM = rapid eye movement; SEI = sleep efficiency index; TST = total sleep time; WASO = wake after sleep onset.

Table 3—MANCOVA comparisons for processing speed and attention.

	FEP (n = 10)	Control (n = 19)	*F*	*P*	η^2
SP1, seconds	12.23 ± 4.45	8.04 ± 1.13	4.59	.042	.150
SP2, seconds	14.23 ± 6.19	8.58 ± 1.56	3.70	.066	.121
SP3, seconds	19.54 ± 9.20	11.41 ± 1.78	4.62	.041	.149
TMT-A, seconds	65.32 ± 39.13	29.58 ± 14.31	2.94	.099	.099
WAIS-Coding	28.90 ± 12.63	56.36 ± 13.87	11.21	.002*	.301

Values are means ± SDs unless otherwise indicated. *P < .01. FEP = first-episode psychosis; MANCOVA = multivariate analysis of covariance; SP = Stroop; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale test.

Table 4—MANCOVA comparisons for executive functions.

	FEP (n = 10)	Control (n = 18)	*F*	*P*	η^2
SP4, seconds	29.11 ± 19.52	15.24 ± 4.95	2.33	.139	.085
SP5, seconds	38.26 ± 17.38	21.07 ± 6.31	3.94	.058	.136
COWAT category	12.80 ± 5.37	20.00 ± 4.03	4.75	.039	.160
COWAT phonem	15.00 ± 4.52	40.94 ±.13.37	15.35	.001*	.381
TMT-B, seconds	174.74 ± 73.92	69.50 ± 27.73	14.77	.001*	.371

Values are means ± SDs unless otherwise indicated. *P < .01. COWAT = Controlled Oral Word Association Test; FEP = first-episode psychosis; MANCOVA = multivariate analysis of covariance; SP = Stroop; TMT = Trail Making Test.

have reported a reduction in REM latency,[6,18,21] other researchers have reported no change.[73] In the current study, REM parameters did not significantly differ between the participants with psychosis and the control group. However, we found a reduction in the percentage of stage N2 sleep among patients compared with the control group. This finding was contrary to Manoach et al's results.[34] Nevertheless, our findings support the results of a meta-analysis reported by Chouinard et al.[21] In addition, in our study, the increase in positive symptoms was associated with the decrease in percentage of stage N2 sleep, which can be an indicator of a disruption in sleep continuity.

Evidence suggests that there may be a relationship between sleep parameters and the severity of positive and negative symptoms in patients with schizophrenia,[36] which is consistent with the idea that sleep changes play a potential role in the

Table 5—MANCOVA comparisons for memory and learning.

	FEP (n = 15)	Control (n = 19)	*F*	*P*	η^2
AVLT total	34.46 ± 7.13	49.31 ± 6.88	29.09	.000**	.484
AVLT-RI	6.13 ± 2.87	10.47 ± 2.32	21.24	.000**	.407
AVLT-PI	4.20 ± 1.52	5.94 ±.97	11.29	.002*	.267
AVLT-DR	5.26 ± 2.40	9.89 ± 2.51	21.72	.000**	.412
SDLT	3.87 ± 6.40	18.36 ± 4.60	47.42	.000**	.605

Values are means ± SDs unless otherwise indicated. *P < .01; **P < .0001. AVLT = Auditory Verbal Learning Test; DR = delayed recall; FEP = first-episode psychosis; MANCOVA = multivariate analysis of covariance; PI = proactive interference; RI = retroactive interference; SDLT = Serial Digit Learning Test.

Table 6—Characteristics of sleep stages and sleep spindles.

	FEP	Control
Sleep stage,[a] minutes		
N1 duration	49.82 ± 22.07	41.78 ± 12.58
N2 duration	177.76 ± 31.04	209.33 ± 23.44
N3 duration	76.61 ± 29.60	85.41 ± 22.79
REM	84.30 ± 38.23	71.90 ± 17.69
Sleep spindles[b]		
Spindle amplitude, mV	36.41 ± 1.68	38.19 ± 1.72
Spindle peak frequency, Hz	13.09 ± 0.40	13.15 ± 0.49
Spindle mean frequency, Hz	12.84 ± 0.97	12.71 ± 0.95
Spindle duration, seconds	1.094 ± 0.037	0.969 ± 0.036

Values are means ± SDs. FEP = first-episode psychosis; N = non–rapid eye movement; REM = rapid eye movement. [a]FEP, n = 21; Control, n = 21. [b]FEP, n = 21; Control, n = 19.

Table 7—Pearson correlations between sleep parameters, neuropsychological tests, and PANSS.

	PANSS 1(+): 20.65 ± 4.24	PANSS 2(−): 25.71 ± 5.31
Sleep latency	−.519*	.227
N1%	−.238	.464*
N2%	−.476*	−.001
N3%	.373	−.461*
AVLT total	.605*	−.529
AVLT 5	.509	−.561*
SDLT	.781**	−.537*
SP5	−.544*	.250
COWAT category	.865***	−.592*

*P < .05, **P < .01, ***P < .001. AVLT = Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; PANSS = Positive and Negative Syndrome Scale; N = non–rapid eye movement; SDLT = Serial Digit Learning Test; SP = Stroop.

Table 8—Pearson correlations between neuropsychological tests and sleep parameters.

	Sleep Latency	N1%	N2%	N3%
AVLT total (n = 15)	−.618*	−.252	−.106	−.076
AVLT delayed recall (n = 15)	−.543*	−.484	−.286	.219
SDLT (n = 16)	−.187	−.294	−.361	.604*
COWAT category (n = 13)	−.553	−.568*	−.243	.578 *
SP5 (n = 16)	.326	.063	.062	−.558*

*P < .05. AVLT = Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; N = non–rapid eye movement; SDLT = Serial Digit Learning Test; SP = Stroop.

pathophysiology of the disorder.[2,54,59] In previous studies, negative correlations were obtained between negative symptoms and slow-wave sleep in never-medicated patients with schizophrenia and those who discontinued medication.[74] Consistent with previous findings, we found that, as the negative symptom severity increased, the percentage of stage N3 sleep decreased.

It was previously suggested that decreased slow-wave sleep and increased negative symptoms in schizophrenia were both associated with reduced brain metabolism.[71] In the healthy brain, these rhythms reflect and participate in plastic processes during sleep.[75] In accordance with this view, we found that negative symptoms were negatively correlated with verbal memory, learning, mental flexibility, verbal fluency, and semantic organization. The reduction in stage N3 sleep was also associated with impairments in learning, verbal fluency, and response inhibition. Additionally, increment in sleep latency was associated with poor performance in encoding and recall. Prefrontal cortical pathway abnormalities in schizophrenia have been hypothesized as one of the causes for these deficits of cognitive functioning and sleep.[56,74] These deficits are associated with a range of molecular and morphological alterations, which, in turn, reflect disrupted neuroplasticity function of the brain.[78]

It is known that prefrontal areas have a critical role in slow-wave sleep; thus, dysfunction in this area is considered to have an effect both on stage N3 sleep and cognitive functions governed by this area.[24,77,78] The association between negative symptoms and cognitive impairments in patients with FEP has been consistently reported.[79,80] Our findings are consistent with previous study findings and support the hypothesis that, compared with positive symptoms, negative symptoms are more closely related to deficits in higher cognitive functions.[80,81] A negative correlation was observed between negative symptoms and scores of subtests evaluating learning and memory, as mentioned above. The atrophy of gray matter and dysconnectivity of white matter in frontal and temporal areas and in thalamocortical networks have been commonly reported in schizophrenia.[75,81]

In the current study, neuropsychological test scores including processing speed, learning memory, and executive functions (working memory, verbal fluency) were significantly low in the FEP group compared with the control group. On the other hand, the Trail Making Test A form that was used to measure psychomotor speed and visual scanning and the Stroop test TBAG that was used to measure reading speed, focused attention, and response inhibition (although a correlation was found between SP5 and stage N3 sleep) did not differ significantly between groups. In contrast, the other form of the test, which was used to assess executive functions (working memory), was performed significantly worse in the FEP group than in the control group. We can conclude that attention and processing speed may be preserved when impairment of higher cognitive functions, such as memory, executive functions, and learning, occur or exist around the time of the onset of the clinical symptoms.

The other sleep parameter we have focused on was sleep spindles, which were found to be altered in the FEP group.[82] We found a reduction in spindle density in a well-controlled study. Likewise, Kaskie et al[83] found that patients with FEP showed reduced spindle duration and density but found no reduction in spindle amplitude when compared with the healthy control group. In addition, the reduction in spindle density was found to be localized in the frontal area and it predicted the severity of the patients' negative symptoms. Sleep spindles are generated within a well-understood circuitry where the thalamocortical connections play a central role. Our study results revealed that this circuitry was somewhat changed in FEP. Manoach et al[34] proposed sleep spindles as a potential novel endophenotype and target for research and treatment development. It was suggested that sleep spindles may serve as a novel treatment biomarker associated with cognition.[84] However, Baandrup et al[85] found no association between cognitive functioning and sleep spindle density or sleep spindle morphology for spindles in non-REM sleep when controlling for sex, age, symptom severity, and daily dose of antipsychotics and benzodiazepines. Similarly, we did not find any relationship between spindle parameters and neuropsychological scores. We can conclude that the impairment in cognitive functions and spindle parameters may differ nonlinearly between patients in our research group.

With regard to FEP, schizophrenia, and sleep, inconsistent results have been reported in the literature. This was attributed to the heterogeneity of the disorder, effects of drugs, duration of the illness, age of patients, sampling procedures, first-night effect of the sleep laboratory, and comorbid primary sleep disorders.[2] These limitations were considered in the design of the current study to minimize possible confounding variables.

The main limitations of the current study were as follows: (1) the 6-month follow-up session, which was necessary to make a definitive clinical diagnosis, could not be performed for 5 of the patients; (2) patients who were considered to have a higher possibility of completing the sleep recording procedures were primarily preferred for inclusion in the study; (3) the neuropsychological test battery was not applied to all participants due to fatigue or reluctance.

According to a recent study, sleep disorders were found to be associated with paranoia, hallucinations, and cognitive disorganization in patients with nonaffective psychosis.[54] Based on the current study and analysis we conclude that the results regarding cognitive functions and sleep in FEP are important in understanding the underlying mechanisms of schizophrenia. Taken together, these findings suggest that patients with FEP show global cognitive impairment (except for attention and processing speed), which is associated with changes in sleep architecture and severity of negative symptoms. Sleep spindle reduction can be an indicator in understanding the electrophysiological underlying mechanisms of schizophrenia.

ABBREVIATIONS

EEG, electroencephalography
FEP, first-episode psychosis
PANSS, Positive and Negative Syndrome Scale
REM, rapid eye movement
TBAG, Temel Bilimler Arastirma Grubu

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ACKNOWLEDGMENTS

The authors thank Professor Hamdullah Aydın and Professor Eyup Akarsu for useful discussions. The authors also thank Dr Emah Kızılay for his contribution to the study. Dr. Yazıhan acknowledges the Department of Interdisciplinary Neuroscience, Ankara University, Ankara, Turkey, where she completed her PhD thesis.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June 21, 2019
Submitted in final revised form August 15, 2020
Accepted for publication August 17, 2020
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DISCLOSURE STATEMENT

The authors state that they have read and approved the final manuscript. Work was for this study was performed at Gulhane Research and Training Hospital, Ankara, Turkey. The authors report no conflicts of interest.