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Original Article

Impairment of sleep-related memory consolidation in schizophrenia: relevance of sleep spindles?

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ABSTRACT

Objectives: Deficits in declarative memory performance are among the most severe neuropsychological impairments in schizophrenia and contribute to poor clinical outcomes. The importance of sleep for brain plasticity and memory consolidation is widely accepted, and sleep spindles seem to play an important role in these processes. The aim of this study was to test the associations of sleep spindles and picture memory consolidation in patients with schizophrenia and healthy controls.
Methods: We studied 16 patients with schizophrenia on stable antipsychotic medication (mean age ± standard deviation, 29.4 ± 6.4 years) and 16 healthy controls matched for age and educational level. Sleep was recorded and scored according to American Academy of Sleep Medicine (AASM) standard criteria. We performed a picture recognition paradigm and compared recognition performance for neutral and emotional pictures in sleep and wake conditions.
Results: Recognition accuracy was better in healthy controls than in patients with schizophrenia in the sleep and wake conditions. However, the memory-promoting effect of sleep was significantly lower in schizophrenia patients than in controls. Sleep spindle activity was reduced in patients, and sleep spindle density was correlated with sleep-associated facilitation of recognition accuracy for neutral pictures.
Conclusion: Reduced sleep spindles seem to play an important role as a possible mechanism or biomarker for impaired sleep-related memory consolidation in patients with schizophrenia, and are a new target for treatment to improve memory functions and clinical outcomes in these patients.

1. Introduction

The importance of sleep for brain plasticity and memory consolidation is widely accepted [1,2]. Concerning the question of how consolidation occurs in sleep, two hypotheses have been recently developed and discussed. The "synaptic homeostasis hypothesis" proposes that a down-scaling of synapses during sleep would improve the signal-to-noise ratio of memory traces and thereby lead to memory consolidation [3]. Central to the "active system consolidation" hypothesis is the assumption that memory consolidation during sleep originates from the repeated reactivation of newly encoded memory representations driven by slow oscillations and accompanied by hippocampal sharp wave-ripples and thalamocortical sleep spindles [4].

A sleep spindle is a train of distinct waves with a frequency of 11–16 Hz and a duration of ≥0.5 s [5]. Sleep spindle activity has been reported to increase after episodic learning [6] and positively predicts improvement of memory recall the next morning [7,8]. However, there are also counter-examples that indicate no positive correlations between sleep spindles and overnight performance improvement in a declarative memory task [9]. In a recent study, spindle density during stage 2 sleep after encoding positively correlated with recognition of pictures six days later [10]. It remains a matter of debate, however, whether spindles per se are important for learning or whether spindling propensity merely reflects the efficiency and the connectivity of the thalamocortical system [11].

Schizophrenia is a severe brain disorder characterized by positive symptoms such as delusions and hallucinations, negative symptoms such as affective flattening and avolition, and cognitive symptoms, such as memory deficits. A range of neurotransmitter systems is affected in this disorder, many of which overlap with those involved in sleep regulation [12]. Sleep disturbances in schizophrenia include sleep fragmentation and decreases in sleep efficiency. A reduction in slow-wave sleep duration or slow-wave activity has often been reported [13,14] but not consistently observed [15].

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Recently it was described that patients with schizophrenia have a marked reduction in sleep spindles compared to healthy controls [16,17], and these reductions were found to correlate with deficits in procedural memory [17]. In an earlier nap study, we also found a decrease in spindle density in schizophrenia patients in comparison to healthy controls and patients with major depression, and a lack of sleep-associated improvement in a procedural memory task. However, no significant correlation between spindle deficits and learning performance was found in this study [18].

Impaired hippocampus-dependent declarative memory belongs to the pronounced cognitive deficits in schizophrenia [19]. Concerning verbal declarative memory, dysfunctions are caused by impairment of encoding and also by storage deficits [20]. Verbal declarative memory appears to be one of the strongest markers of functional outcome in patients [21,22]. Therefore the aim of this study was to test associations of sleep spindles and declarative memory consolidation in schizophrenia patients and healthy controls. We performed a picture recognition paradigm and compared performance in sleep and wake conditions. We used neutral and emotional pictures, because different mechanisms are believed to be involved in neutral and emotional memory consolidation processes [4]. We hypothesized that there would be less sleep-related memory consolidation in schizophrenia and a correlation of reduced sleep spindles with recognition accuracy for pictures.

2. Methods

2.1. Study participants

A total of 34 subjects were originally recruited: 16 patients with schizophrenia, as diagnosed according to the International Classification of Diseases, 10th Edition (ICD-10) (subtypes: paranoid [n = 14] and schizoaffective [n = 2]) and 18 healthy controls, matched for age and education (Table 1). Two healthy subjects had to be excluded from the data analysis, one because of a sleep apnea syndrome (apnea–hypopnea index > 5/h) and one because of short sleep duration (<5 h).

The age of the 16 patients ranged from 20 to 42 years, with a mean ± standard deviation (SD) of 29.4 ± 6.4 years (seven female and nine male patients; 13 inpatients). The mean total score of the Positive and Negative Syndrome Scale (PANSS) [23] was 57 ± 8, corresponding to a prevailing mild symptomatology of clinically stable patients with a mean illness duration of 6 ± 4 years. All patients were on stable antipsychotic medication that was unchanged during the study and that consisted mostly of atypical antipsychotics (n = 15); one patient took the typical antipsychotic flupenthixol. Five patients received concomitant psychopharmacological medication with citalopram (n = 2), promethazine (n = 1), biperiden (n = 1), and lorazepam (n = 1). Any relevant additional medical condition was assessed by medical history, physical examination, and routine laboratory investigation. Exclusion criteria were primary substance abuse, mental retardation, and acute or unstable medical problems.

The age of the healthy controls ranged from 19 to 39 years (mean 28.3 ± 6.1 years; nine female). They were recruited from the community by poster and were screened to exclude a personal history of mental illness and psychoactive medication use. Patients and controls did not differ in age, sex, or educational level (Table 1). All participants gave their informed written consent. The study was approved by the local ethics committee and conformed to the principles of the Declaration of Helsinki.

Table 1
Characteristics of study participants.

	Controls (n = 16)	Patients (n = 16)	*p*
Age, y	28.3 ± 6.1	29.4 ± 6.4	0.6
Women/men	9/7	7/9	0.5*
School education, y	10.8 ± 1.3	10.5 ± 1.8	0.7
Sleep quality, PSQI	4.4 ± 2.1	7.3 ± 3.2	**0.005**
Digit span forward, before learning			
Sleep condition, evening	8.8 ± 2.5	8.1 ± 2.1	0.4
Wake condition, morning	8.9 ± 1.8	8.1 ± 1.6	0.2

Descriptive statistics (except women/men) are expressed as mean ± standard deviation. Digit span forward from the Wechsler Memory Scale [21]. Each correct response of two trials of each length beginning with three and up to nine digits was worth one point. PSQI, Pittsburgh Sleep Quality Index (sleep quality in the past 2 weeks). Two-tailed unpaired t-test; significance set at $p < 0.05$. Significant values in bold.
*Pearson χ^2 test.

2.2. Procedure

Memory performance was tested in wake and sleep conditions (separated by an interval of one week and counterbalanced in order). In the wake condition, the learning phase started at 09:00 and the recall phase was conducted 10 hours later at 19:00. In the sleep condition, learning was performed at 21:00 and recall 10 hours later at 07:00. An adaptation night preceded the experimental night to allow acclimatization to the sleep laboratory and to detect severe sleep disorders such as sleep apnea.

Polysomnography for sleep stage scoring was conducted between lights-off (regulated by the patients themselves between 22:00 and 24:00) and lights-on (at 6:30). Electroencephalographic (EEG), electrooculographic (EOG), and submental electromyographic (EMG) activity were measured (Somnomedics, Randersacker, Germany). The EEG montage, according to the 10–20 system, included the positions C4, O2, and F4 all referenced to M1. Electrodes at C3, O1, and F3 all referenced to M2 and were used as backup positions. Recordings were visually scored according to standard American Academy of Sleep Medicine (AASM) criteria [5] by a trained rater. The following parameters were computed: sleep onset latency (in minutes), total sleep time (in minutes), sleep efficiency (ratio of total sleep time to time in bed in percent), number of awakenings, stage 1 sleep (N1), stage 2 sleep (N2), slow-wave sleep (N3), and rapid eye movement (REM) sleep (all in percentage of total sleep time), and REM latency (time from sleep onset to the first epoch of REM sleep in minutes). Sleep spindles in stage 2 sleep of the entire night were detected and counted by a technical assistant unaware of the study objective. Automatic detection by our sleep analyzing system (Somnomedics) marked events in the C4-M1 recording, which fulfilled the following criteria: frequency 11–16 Hz, duration 0.5–8 s, amplitude 5–300 μV, and a relative change from baseline amplitude of >250%. The highlighted events were manually checked by a technical assistant and counted as sleep spindles if they fulfilled the AASM criteria (frequency of 11–16 Hz and duration of ≥0.5 s), and also showed a typical waxing and waning morphology [11]. Sleep spindles were evaluated by a trained technical assistant unaware of the hypotheses of the study.

EEG spectral power was obtained from C3 and C4, which were referenced against the mean of M1 and M2. The fast Fourier transform (FFT) algorithm was performed using Brain Vision Analyzer 2 (Brain Products, Germany). Only artifact-free epochs of 8-s duration were analyzed, and the truncating error was reduced by a Hanning window. The log-transformed absolute power values for delta (δ; 1–4 Hz), theta (θ; 4–8 Hz), alpha (α; 8–12 Hz), and sigma (σ; 12–16 Hz) during stage 2 sleep were used for further analyses.

Before the learning phase, digit span forward was used as a control for short-term memory. The digit span procedure was adopted from the Wechsler Memory Scale [24]. We used digit span forward beginning with three and up to nine digits only. Two different trials of each length were conducted until failure on both trials of a span length. Each correct response was worth one point, with

a maximum of 14 points. Subjective sleep quality was assessed by a five-point analogue scale (1 = very bad to 5 = very good).

2.3. Memory task

Stimuli were two sets, each consisting of 220 pictures (110 neutral and 110 negative emotional). The majority were taken from the International Affective Picture System (IAPS) [25], whereas some were chosen from an in-house picture set that included images similar to the IAPS set [26]. Both picture sets were parallelized with respect to arousal and valence ratings. The order of the picture sets in the wake and sleep conditions was balanced. During the learning phase, 110 pictures (55 emotional and 55 neutral) were presented on a computer screen for 1.5 s each. The retention interval (sleep or 10 hours of wakefulness) was followed by the recognition test, in which 220 pictures were shown for 1.5 s each, and the participants were asked for an "old"/"new" judgment. The 110 targets from the learning phase (55 emotional and 55 neutral) were mixed with 110 previously unseen distracters (55 emotional and 55 neutral). To correct for response bias, the dependent variable recognition accuracy was calculated as the difference between the hit rate (proportion of correctly recognized old pictures of all old pictures) and the false alarm rate (proportion of incorrectly recognized new pictures of all new pictures) [27].

2.4. Statistical analysis

Descriptive statistics are expressed as mean ± SD. Recognition accuracy was analyzed based on a mixed analyses of variance with a between-subjects factor GROUP (controls vs patients) and the within-subjects factors CONDITION (sleep vs wake) and AFFECT (neutral vs emotional). To assess differences in sleep stages and sleep spindle density between schizophrenia patients and controls, single means were compared using a Student t-test for independent samples. Correlations between recognition accuracy and sleep parameters were performed by Pearson correlation coefficients. The level of significance was set at 5%. Data analysis was performed with SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY).

3. Results

3.1. Memory performance

The analyses of recognition accuracy revealed a main effect GROUP, indicating an overall reduced accuracy in patients with schizophrenia (SZ) compared to controls (CTR) (SZ: 0.54 ± 0.11; CTR: 0.70 ± 0.10; SZ vs CTR: $F_{1,30} = 27.2$, $p < 0.001$). The main effect CONDITION indicated that sleep resulted in an enhanced recognition accuracy compared to wake (sleep: 0.66 ± 0.14; wake: 0.58 ± 0.12; sleep vs wake: $F_{1,30} = 24.7$, $p < 0.001$). The interaction between GROUP and CONDITION ($F_{1,30} = 5.3$, $p = 0.029$) reached significance, and subsequent t-tests revealed that sleep in patients with schizophrenia did not enhance recognition accuracy ($t_{15} = 1.8$, $p = 0.091$) to the extent observed in healthy controls ($t_{15} = 5.4$, $p < 0.001$] (Fig. 1). Overall, there was a memory bias for emotional stimuli such that emotional pictures were better recognized than neutral pictures (emotional pictures: 0.65 ± 0.11; neutral pictures 0.59 ± 0.12; $F_{1,30} = 16.0$, $p < 0.001$). However, neither the interaction AFFECT × GROUP ($p = 0.148$) nor the interaction CONDITION × AFFECT × GROUP ($p = 0.828$) was significant. To look for possible effects of emotional stimulus material on sleep-related memory performance, exploratory t-tests were performed (Table 2). However, because of the lack of significant interactions with respect to the factor AFFECT, we refrained from any further interpretation. As shown by a z-transformation, the two patients with schizoaffective disorder did not display deviant sleep-dependent memory performance within the patient group (–1.5 < z < 1.5). One-sample t-tests revealed that in each condition (sleep/wake, emotional/neutral) patients as well as healthy controls recognized pictures better than chance (for all comparisons: test value = 0; t > 14.1, $p < 0.001$).

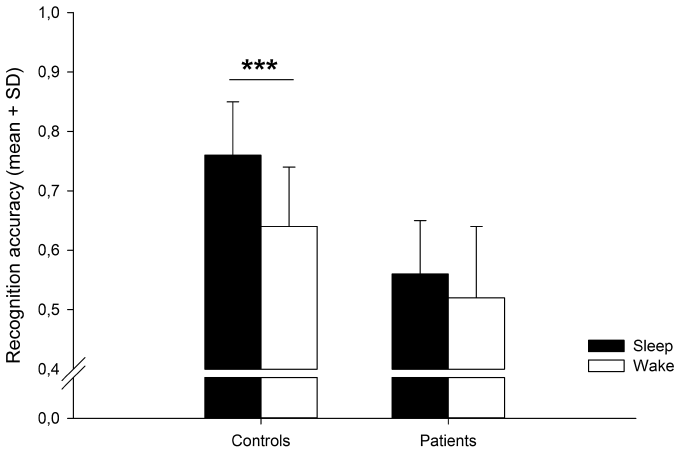

Fig. 1. Recognition accuracy 10 hours after learning of pictures in control subjects and patients with schizophrenia in a sleep and wake condition.

3.2. Sleep parameters

As shown in Table 3, patients with schizophrenia showed a significantly longer time in bed and total sleep time than controls. Patients and controls did not differ in sleep architecture, which was measured as the percentage of total sleep time spent in any sleep stage. Schizophrenia patients exhibited markedly reduced sleep spindle density to less than 50% compared to controls ($p < 0.001$; Table 3). During stage 2 sleep (N2), patients with schizophrenia only showed a decrease in sigma power (12–16 Hz, $p < 0.001$; Table 3) but no deviant activity in other frequency ranges ($p > 0.4$).

3.3. Correlations between sleep spindles and recognition accuracy

There were significant correlations between recognition accuracy for neutral (but not emotional) pictures and sleep spindle density in the experimental night before recall in healthy controls (Table 4). As a measure of enhanced memory consolidation due to sleep, the difference in recognition accuracy in the sleep versus wake condition was calculated. The amount of enhanced memory performance by sleep was significantly correlated with sleep spindle density of stage 2 sleep in healthy controls (electrodes C3 and C4) and also in patients with schizophrenia (only C4) with respect to

Table 2
Picture recognition accuracy.

Characteristic	Controls (n = 16)	Patients (n = 16)	p
Sleep condition			
Neutral	0.75 ± 0.11	0.53 ± 0.10	**<0.001**
Emotional	0.77 ± 0.10	0.59 ± 0.10	**<0.001**
Combined	0.76 ± 0.09	0.56 ± 0.09	**<0.001**
Wake condition			
Neutral	0.62 ± 0.13	0.46 ± 0.13	**0.002**
Emotional	0.67 ± 0.08	0.57 ± 0.14	**0.03**
Combined	0.64 ± 0.10	0.52 ± 0.12	**0.003**
Sleep vs wake condition			
Neutral	0.14 ± 0.13	0.06 ± 0.11	0.11
Emotional	0.10 ± 0.11	0.02 ± 0.12	0.06
Combined	0.12 ± 0.09	0.04 ± 0.10	**0.03**

Recognition accuracy (hit rates – false alarm rates).
Two-tailed unpaired t-test; significance set at $p < 0.05$. Significant values in bold.

Table 3
Sleep parameters in study sample.

Characteristic	Controls (n = 16)	Patients (n = 16)	*p*
Time in bed, min	442 ± 61	498 ± 59	**0.01**
Sleep onset latency, min	21.0 ± 17.6	34.6 ± 35.3	0.2
Total sleep time, min	369.7 ± 42.2	428.7 ± 72.9	**0.01**
Sleep efficiency, %	86.6 ± 7.8	85.8 ± 8.9	0.8
Number of awakenings	15.7 ± 4.4	12.6 ± 10.3	0.3
Stage 1 sleep, %	11.5 ± 4.2	12.0 ± 8.3	0.8
Stage 2 sleep, %	49.9 ± 7.6	51.8 ± 8.4	0.5
SWS, %	20.0 ± 7.2	15.8 ± 9.5	0.2
REM sleep, %	18.6 ± 4.6	20.5 ± 5.1	0.3
REM density, %	11.0 ± 4.0	14.1 ± 6.7	0.13
Sleep spindle density			
C3	4.1 ± 1.4	1.9 ± 1.0	**<0.001**
C4	3.7 ± 1.4	1.7 ± 1.1	**<0.001**
Spectral power (C3) during stage 2 sleep, μV^2			
Delta (δ; 14 Hz)	4.56 ± 0.4	4.07 ± 0.4	0.4
Theta (θ; 4–8 Hz)	0.66 ± 0.07	0.66 ± 0.08	0.97
Alpha (α; 8–12 Hz)	0.35 ± 0.04	0.30 ± 0.04	0.4
Sigma (σ; 12–16 Hz)	0.24 ± 0.02	0.12 ± 0.01	**<0.001**
Subjective sleep quality	3.4 ± 0.9	3.9 ± 0.8	0.16

Sleep spindle density: Number of sleep spindles during stage 2 sleep per minute of stage 2 sleep. C4: derivation C4-M1; C3: derivation C3-M2. Subjective sleep quality (1 = very bad to 5 = very good). REM, rapid eye movement. SWS, slow-wave sleep. Two-tailed unpaired t-test; significance set at $p < 0.05$. Significant values in bold.

Table 4
Correlations between sleep spindle density and recognition accuracy.

Characteristic	Controls (n = 16)		Patients (n = 16)	
	C3	C4	C3	C4
Sleep condition				
Neutral	0.60*	0.61*	0.34	0.35
Emotional	0.04	0.06	0.02	0.03
Combined	0.39	0.40	0.17	0.21
Sleep vs. wake				
Neutral	0.64**	0.57*	0.48 (*)	0.58*
Emotional	–0.12	–0.13	–0.04	0.09
Combined	0.39	0.33	0.25	0.39

Pearson correlations.
*Significance set at $p < 0.05$; **significance at $p < 0.01$; (*) statistical trend at $p < 0.1$.

neutral pictures. Concerning electrode C3, the correlation between sleep spindle density and memory performance in the patients group failed to reach significance but showed a statistical trend ($p = 0.058$). In Fig. 2 is shown the sleep-associated enhancement of picture recognition as a function of spindle density in patients with schizophrenia and control participants (Fig. 2). Regarding other non-REM sleep or REM sleep parameters, no significant correlation with recognition accuracy was found. There were also no significant correlations between sleep spindle density and measures concerning the psychopathology of the patients (PANSS; data not shown).

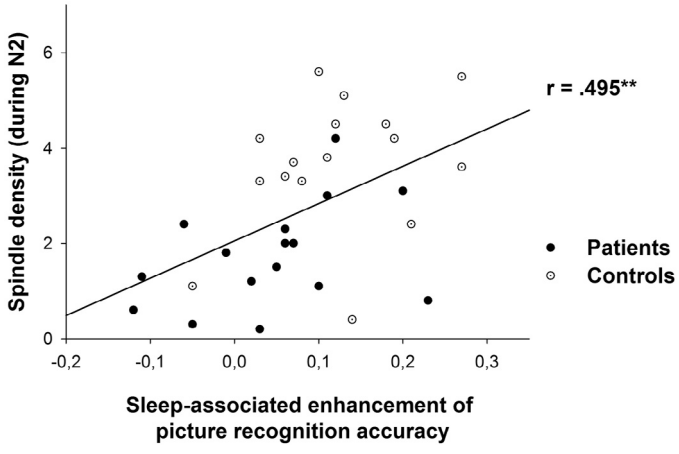

Fig. 2. Sleep-associated enhancement of picture recognition as a function of spindle density in patients with schizophrenia and control participants. Spindle density is shown as the number of spindles per minute during stage 2 sleep (C4 electrode).

4. Discussion

The main results of the present study were as follows: (1) The memory promoting effect of sleep was significantly lower in schizophrenia patients than in healthy controls; (2) patients with schizophrenia showed a marked decrease of sleep spindles; and (3) significant correlations between sleep spindle density and sleep-dependent enhancement of neutral declarative memory were found in both patients and healthy controls.

Essential aspects of recent research on sleep-dependent memory consolidation in healthy individuals and those with disorders could thereby be replicated by our study. A lack of improvement in memory performance after sleep in schizophrenia patients in contrast to healthy controls was already seen in earlier studies concerning procedural and motor learning [17,18]. One strength of this study is the comparison of comparable declarative memory tests in sleep and wake conditions. Thus, a clear memory-promoting effect of sleep was shown in healthy subjects, but not in patients with schizophrenia. Independent of the fact that memory performance in schizophrenia is decreased even in a normal wake condition [19], there is no further memory-enhancing effect of sleep in this disorder. According to this result, the mechanisms of memory consolidation during sleep must be additionally disturbed in schizophrenia, and impaired generation of sleep spindles seems to be an interesting link to this.

The thalamic reticular nucleus acts as a spindle pacemaker [28], but corticothalamic feedback is believed to aid long-range spindle synchrony and contributes to the termination of spindles by desynchronizing thalamic activity [29,30]. In several [16–18] but not all [31] studies, a marked decrease in sleep spindles in schizophrenia was described. In our study, again, a significant (~50%) reduction in sleep spindles in schizophrenia patients was observed. The underlying cause of this spindle phenotype in schizophrenia is unclear [32]. Thalamic dysfunctions [16,33] were accounted for this, but, since the cortex also plays a crucial role in generating spindles, a cortical contribution to the spindle deficit in schizophrenia is possible [32]. Convenient with the above-mentioned hypotheses about possible functions of sleep spindles, associations between the reduced density of spindles and decreased performance in procedural learning [17] and in our study with impaired sleep-related declarative memory performance were found.

As mentioned in the Introduction, it is still unclear whether spindles per se are important for memory consolidation or whether they only reflect the connectivity of the thalamo-cortical system [11]. Supporting the first assumption, there are indications that spindles facilitate long-term plasticity processes, possibly by generating a Ca^{2+} entry in cortical dendrites [34]. Repeated spindle-like spike discharges have been found to trigger long-term potentiation in neocortical synapses in in vitro models [35]. In this context, it would be comprehensible that a simple reduction in the number or density of sleep spindles in schizophrenia patients, for example, could be sufficient to impair sleep-related memory consolidation. In addition, a disturbed coordination of hippocampal ripples and thalamocortical spindles, as seen in a rat model of schizophrenia [36], might further contribute to decreased memory consolidation during sleep. In simultaneous EEG and functional magnetic resonance imaging measurements during stage 2 sleep spindles, an increased connectivity between hippocampal formation and neocortex was observed [37]. The interpretation of decreased sleep

spindles as a biomarker for decreased connectivity fits well with a description of schizophrenia as a disease of "reduced synaptic connectivity" [38,39].

With regard to positive symptoms of patients with schizophrenia, reduced sleep spindles were recently linked to a failure of source monitoring of own thoughts and actions to an outside agency leading to symptoms such as hallucinations and delusions. This failure in source monitoring was attributed to a failure of a brain mechanism called corollary discharge, which allows actions to be recognized as one's own and which also involves the thalamus [40]. However, in our study, we found no correlation between positive symptoms and spindle activity, maybe because of characteristics of our study population with a relatively mild and homogenous symptomatology.

Another interesting aspect of our results is that sleep spindles were significantly correlated with recognition accuracy of neutral pictures but not of emotional pictures. It therefore seems to be that other sleep-related mechanisms, such as coherent theta (θ) activity in the amygdala and prefrontal cortex [41], may contribute to the consolidation of emotional contents.

A limitation of the study is that the patients were treated with a variety of mostly atypical antipsychotics, and some also took concomitant psychopharmacological medication. Six patients received olanzapine, which is known to increase total sleep time and slow-wave sleep [14,42], and which might be why we did not find a lesser amount of slow-wave sleep and an association of slow-wave sleep and memory performance in this patient group as in earlier studies [43]. In a previous study, a single dose of olanzapine was associated with a decrease of about 35% in spindle density [44]. However, in an earlier study, haloperidol had no effect on changes in spindle density [45]. In another study, no spindle abnormalities were found in nonschizophrenia patients receiving antipsychotics, suggesting that medications were unlikely to be responsible for spindle deficits in schizophrenia [16]. In our study, treatment was unchanged within the wake and the sleep conditions, so the main result of a lack of a sleep-promoting effect on declarative memory performance also seems to be independent of medication. Another limitation of the study is that the rater who performed the sleep and spindle scoring was not blinded to the diagnosis of the patients but was, however, blinded to the study objectives.

5. Conclusion

In conclusion, we found further indications of reduced sleep spindles as a biomarker and possibly a mechanism for decreased sleep-related memory consolidation in schizophrenia. Because deficits in declarative memory strongly predict functional long-term outcome in schizophrenia [21,22], compensation of such deficits should be an important goal of clinical efforts, and, given the role of sleep spindles in memory consolidation, they offer a promising potential target for novel treatments. GABA-A agonistic hypnotics such as zolpidem or eszopiclone increased sleep spindle density, and zolpidem resulted in better verbal memory in healthy subjects [46]. In a recent study, eszopiclone increased sleep spindles in patients with schizophrenia, but enhancement of overnight motor task improvement failed to reach significance [47]. However, long-term administration of GABA-A agonistic hypnotics such as zolpidem or zopiclone is controversial in many countries because of cases of development of tolerance and dependency [48]. Another interesting method, which possibly increase neural connectivity and thereby memory consolidation, is the transcranial direct-current stimulation during sleep [49,50]. The further development of electrical or auditory stimulations in phase with the ongoing rhythmic occurrence of slow oscillation up states in sleep [51] offers a promising target to improve memory performance and thereby functional outcome in schizophrenia patients.

Conflict of interest

This was not an industry-supported study. The authors have indicated no financial conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.12.022.

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