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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