Reduced Sleep Spindles and Spindle Coherence in Schizophrenia: Mechanisms of Impaired Memory Consolidation?

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Background: Sleep spindles are thought to induce synaptic changes and thereby contribute to memory consolidation during sleep. Patients with schizophrenia show dramatic reductions of both spindles and sleep-dependent memory consolidation, which may be causally related.

Methods: To examine the relations of sleep spindle activity to sleep-dependent consolidation of motor procedural memory, 21 chronic, medicated schizophrenia outpatients and 17 healthy volunteers underwent polysomnography on two consecutive nights. On the second night, participants were trained on the finger-tapping motor sequence task (MST) at bedtime and tested the following morning. The number, density, frequency, duration, amplitude, spectral content, and coherence of stage 2 sleep spindles were compared between groups and examined in relation to overnight changes in MST performance.

Results: Patients failed to show overnight improvement on the MST and differed significantly from control participants who did improve. Patients also exhibited marked reductions in the density (reduced 38% relative to control participants), number (reduced 36%), and coherence (reduced 19%) of sleep spindles but showed no abnormalities in the morphology of individual spindles or of sleep architecture. In patients, reduced spindle number and density predicted less overnight improvement on the MST. In addition, reduced amplitude and sigma power of individual spindles correlated with greater severity of positive symptoms.

Conclusions: The observed sleep spindle abnormalities implicate thalamocortical network dysfunction in schizophrenia. In addition, the findings suggest that abnormal spindle generation impairs sleep-dependent memory consolidation in schizophrenia, contributes to positive symptoms, and is a promising novel target for the treatment of cognitive deficits in schizophrenia.

Key Words: Memory consolidation, motor skill, procedural learning, schizophrenia, sleep, sleep spindles

Sleep disturbances in schizophrenia have been described since Kraepelin (1) and are a common complaint throughout its course (2), including in the prodrome (3), but the nature of the abnormalities and their relations to the pathophysiology, cognitive deficits, and symptoms of schizophrenia remain poorly understood (4). Several recent studies have reported markedly reduced sleep spindle activity in schizophrenia (5–8). Mediated by thalamocortical circuits, spindles are a defining feature of stage 2 non-rapid eye movement (NREM) sleep, evident in the electroencephalogram (EEG) as brief bursts of 12 Hz to 15 Hz synchronous activity. Animal studies point to spindles as a key mechanism of synaptic plasticity, mediating memory consolidation during sleep (9–12). In humans, spindles correlate with overnight memory consolidation across diverse learning paradigms (13). In schizophrenia, memory deficits are a key neurocognitive abnormality and there is evidence of impaired consolidation across multiple domains (14–16). In particular, schizophrenia patients have marked impairments of sleep-dependent motor procedural memory consolidation (17) in the context of reduced spindle activity (5,8). We conducted a new study to more completely specify the nature of sleep spindle abnormalities in schizophrenia and their relation to deficient sleep-dependent memory consolidation.

The most widely reported sleep architecture abnormalities in schizophrenia—reduced slow wave sleep (18–20) and abnormal rapid eye movement sleep (20–22)—are not consistently observed and have not withstood meta-analyses (23,24). Relatively few studies have gone beyond sleep architecture to examine the EEG spectral characteristics of sleep. Three older studies of unmedicated patients that identified NREM spindles with visual detection at a single EEG channel had contradictory findings. Poulin *et al.* (20) examined spindles in the 12 Hz to 14 Hz range and found no differences between patients ($n = 11$) and control participants. Van Cauter (25) also reported no differences in patients ($n = 9$) compared with control participants. Finally, Hiatt *et al.* (26) found that patients ($n = 5$) showed increased spindle density during a 10-minute NREM segment but did not distinguish between stage 2 and slow wave sleep across participants. In contrast, several recent studies that used automated spindle detection algorithms, a larger number of EEG channels, and larger samples comprised of chronic medicated schizophrenia patients report a dramatic reduction of sleep spindles (5–8). In one of these studies, the spindle deficit was associated with greater severity of positive symptoms and was absent in a nonschizophrenic psychiatric control group treated with antipsychotic medications (7), suggesting that the spindle deficit influences symptom presentation and is not due to treatment with antipsychotic medications. To characterize the functional significance of the sleep spindle deficit in schizophrenia, we examined the relations of spindle activity to overnight consolidation of motor memory and to symptoms.

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We employed the same simple, well-characterized test of motor procedural learning used in our previous studies of schizophrenia, the finger tapping motor sequence task (MST) (27,28). After training on the MST, healthy young participants show significant improvement in speed after a night of sleep but not after an equivalent period of wake (28). In young healthy individuals, overnight improvement on the MST and other simple motor skill tasks correlates with the amount of stage 2 sleep (28) and with the number and density of sleep spindles (29–32). In two studies, we have reported that this overnight improvement is absent in schizophrenia (5,17). Our primary hypothesis was that reduced stage 2 sleep spindle activity would correlate with impaired overnight memory consolidation in schizophrenia. We also expected patients to show reduced spindle coherence during sleep based on evidence of reduced EEG coherence during quiet awake (33–36) and dysconnectivity in thalamocortical networks in schizophrenia (37–39).

Methods and Materials

Participants

Twenty-five schizophrenia outpatients were recruited from an urban mental health center and 21 completed the study. Patients had been maintained on stable doses of atypical antipsychotic medications for at least 6 weeks and 12 took diverse adjunctive medications for anxiety, agitation, and/or concurrent mood disturbance (Table S1 in Supplement 1). Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (40) and symptoms were rated with the Positive and Negative Syndrome Scale (PANSS) (41).

Twenty-one healthy control participants, screened to exclude a personal history of mental illness, family history of schizophrenia spectrum disorder, and psychoactive medication use, were recruited from the community by poster and website advertisements and 18 completed the study.

All participants were screened to exclude diagnosed sleep disorders, treatment with sleep medications, a history of significant head injury, neurological illness, and substance abuse or dependence within the past 6 months. One control participant was excluded for sleeping less than 4 hours on two of the five nights preceding the laboratory visit based on wrist actigraphy and sleep log data. The final sample of 21 schizophrenia and 17 control participants did not differ in age, sex, or parental education (Table S2 in Supplement 1). All participants gave written informed consent. The study was approved by the Institutional Review Boards of Massachusetts General Hospital, the Massachusetts Department of Mental Health, and Beth Israel Deaconess Medical Center.

Procedures

In the week before their stay in the Clinical Research Center (CRC), participants completed informed consent, demographic questionnaires, and rating scales; toured the CRC; and received an actigraph to wear until study completion. Participants also completed home sleep logs.

Participants spent 2 consecutive weeknights in the CRC with polysomnography (PSG) and engaged in their usual activities during the day. On the second night, participants were trained on the MST 1 hour before their usual bedtime, wired for PSG, and allowed to sleep for up to 10 hours. They were tested on the MST 1 hour after awakening.

Polysomnography. Data were digitally acquired at 100 Hz using an Embla N7000 system (Medcare Systems, Buffalo, New York) with a standard montage including five to eight channels of EEG (F3, F4, C3, Cz, C4, Pz, O1, O2) referenced to the linked mastoids, electromyography, and electro-oculography. Data from all available electrodes were analyzed for each participant.

Finger Tapping Motor Sequence Task. The MST involves pressing four numerically labeled keys on a standard computer keyboard with the fingers of the left hand, repeating a five-element sequence (4-1-3-2-4) "as quickly and accurately as possible" for 30 seconds. The numeric sequence was displayed at the top of the screen, and dots appeared beneath it with each keystroke. During both training and test sessions, participants alternated tapping and resting for 30 seconds for a total of 12 tapping trials. The primary outcome measure was the number of correct sequences per trial, which reflects both the speed and accuracy of performance. Practice-dependent improvement was defined as the percent increase in correct sequences from the first training trial to the average of the last three training trials. Overnight improvement was calculated as the percent increase in correct sequences from the last three training trials to the first three test trials the following morning (27).

Actigraphy. The Mini-Mitter Actiwatch-64 (Philips Respironics, Bend, Oregon) records wrist movement in 15-second epochs to provide estimates of sleep time based on periods of wrist immobility. Standard scoring algorithms were used to determine time in bed (TIB), total sleep time (TST), and sleep efficiency (TST/TIB).

Data Analysis

As none of the sleep architecture or spindle measures differed significantly across the two laboratory nights in either group, data are presented as an average across both nights. Unless otherwise specified, EEG data are averaged across all electrode sites.

Sleep Architecture. Each 30-second epoch of PSG sleep was visually classified into stages (wake, 1, 2, 3, 4, and rapid eye movement) according to standard criteria (42) by raters blind to diagnosis and night. Awakenings were scored when one or more 30-second epoch was classified as wake following initial sleep onset. Sleep stages are reported as the percentage of TST.

Spindle Analyses. We analyzed spindles during stage 2 sleep, given our primary hypothesis of a relation of stage 2 sleep spindles with memory consolidation. Polysomnography data were preprocessed and analyzed using BrainVision Analyzer 2.0 (BrainProducts, Munich, Germany) and MatLab R2009b (The MathWorks, Natick, Massachusetts). Artifacts were automatically detected and removed and EEG data were filtered at .5 Hz to 35 Hz. Artifact rejection was confirmed by visual inspection.

Power spectral density (μV^2/Hz) was calculated by Fast Fourier Transform (FFT), applying a Hanning window to successive 3-second epochs of stage 2 sleep with 50% overlap. Sigma band (12–15 Hz) spectral power, which correlates with sleep spindle activity, was divided into low (12–13.5 Hz) and high (13.5–15 Hz) sigma band power (43,44).

Discrete sleep spindle events were automatically detected using a wavelet-based algorithm. The raw EEG signal was subjected to a time-frequency transformation using an 8-parameter complex Morlet wavelet (45). Spindles were detected at each EEG channel by applying a thresholding algorithm to the extracted wavelet scale corresponding approximately to the 10 Hz to 16 Hz frequency range. For thresholding, the rectified moving average of the signal was first calculated, using a 100-millisecond sliding window. A spindle event was identified whenever this wavelet signal exceeded threshold (defined as 4.5 times the mean signal amplitude of all artifact-free epochs) for a minimum of 400 milliseconds. This method was validated by examining the correlation of algorithmically detected spindle density with hand-counted spindles in 10