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Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages

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ABSTRACT

We previously reported that patients with schizophrenia failed to demonstrate normal sleep-dependent improvement in motor procedural learning. Here, we tested whether this failure was associated with the duration of Stage 2 sleep in the last quartile of the night (S2q4) and with spindle activity during this epoch. Fourteen patients with schizophrenia and 15 demographically matched controls performed a motor sequence task (MST) before and after a night of polysomnographically monitored sleep. Patients showed no significant overnight task improvement and significantly less than controls, who did show significant improvement. While there were no group differences in overall sleep architecture, patients showed significant reductions in fast sigma frequency power (45%) and in spindle density (43%) during S2q4 sleep at the electrode proximal to the motor cortex controlling the hand that performed the MST. Although spindle activity did not correlate with overnight improvement in either group, S2q4 sleep duration in patients significantly correlated with the plateau level of overnight improvement seen at the end of the morning testing session, and slow wave sleep (SWS) duration correlated with the delay in reaching this plateau. SWS and S2q4 sleep each predicted the initial level of overnight improvement in schizophrenia, and their product explained 77% of the variance, suggesting that both sleep stages are necessary for consolidation. These findings replicate our prior observation of reduced sleep-dependent consolidation of motor procedural learning in schizophrenia and link this deficit to specific sleep stages. They provide further evidence that sleep is an important contributor to cognitive deficits in schizophrenia.

1. Introduction

Sleep disturbances in schizophrenia have been described since Kraepelin (1919) and are associated with poor coping skills and diminished quality of life (Goldman et al., 1996; Hofstetter et al., 2005). Accumulating evidence suggests that abnormal sleep also contributes to cognitive deficits in schizophrenia (e.g., Forest et al., 2007; Goder et al., 2004, 2008; Yang and Winkelman, 2006). In a prior study, we reported that chronic medicated patients with schizophrenia failed to demonstrate normal improvements in procedural learning after a night of sleep, in spite of showing intact practice-dependent learning during training the previous day (Manoach et al., 2004). The goal of the present study was to determine whether this reduced overnight consolidation of procedural learning in schizophrenia is associated with alterations in specific sleep stages or their characteristics, which could provide insight into the mechanisms underlying this cognitive deficit.

Subjective sleep disturbance is common in patients with schizophrenia and often presages psychotic decompensation (Benson, 2006; Lieberman et al., 2005). The presence of sleep abnormalities in antipsychotic-naïve and unmedicated patients indicates that abnormal sleep is not merely a side-effect of medications (for meta-analysis see Chouinard et al. (2004)). While there are reports of diverse abnormalities of sleep architecture in schizophrenia, reduced slow wave sleep (SWS) is the most consistent (e.g., Keshavan et al., 1998; Monti and Monti, 2004; Yang and Winkelman, 2006), but not universal (e.g., Chouinard et al., 2004; Lauer et al., 1997), finding. In spite of its ubiquity, abnormal sleep has generally been overlooked as a potential contributor to cognitive deficits in schizophrenia. This neglect may stem from a tendency to regard disturbed sleep as secondary to other factors and from difficulty

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specifying the exact nature of the disturbance. There is now overwhelming evidence that sleep plays a critical role in memory consolidation (e.g., Stickgold, 2005) and recent studies of schizophrenia report associations between sleep and cognitive performance in medicated (Goder et al., 2004, 2008) and antipsychotic-naïve (Forest et al., 2007) patients. These findings support the hypothesis that abnormal sleep contributes to cognitive deficits in schizophrenia and highlight the need for further study.

In the present study, we employed the same simple, well-characterized test of motor skill learning, the finger tapping motor sequence test (MST) (Karni et al., 1998; Walker et al., 2002) that we used in our previous study of schizophrenia (Manoach et al., 2004). When healthy young participants are trained on this task, they show significant improvements in speed after a night of sleep, but not after an equivalent period of daytime wake (Walker et al., 2002). Additional nights of sleep lead to more improvement, even with no additional practice (Walker et al., 2003b), but sleep deprivation the first night after training blocks all subsequent non-practice related improvement (Fischer et al., 2002). These findings demonstrate that overnight improvement on this task depends on sleep rather than the mere passage of time. Sleep following MST training also leads to increased functional MRI activation in right primary motor cortex, contralateral to the hand performing the task, and to decreased activation in regions that mediate the conscious monitoring of performance (Walker et al., 2005). These and other findings suggest that sleep-dependent consolidation leads to task automation, resulting in performance that is faster, less variable, and less dependent on voluntary attention (Atienza et al., 2004; Kuriyama et al., 2004; Walker et al., 2005).

Overnight improvement on the MST and other simple motor skill tasks specifically correlates with the amount of Stage 2 sleep in the last quartile of the night (S2q4, Fogel et al., 2007; Smith and MacNeill, 1994; Walker et al., 2002). MST improvement also correlates with the number and density of fast spindles (Rasch et al., 2008), and since the MST is performed with the left hand, it is interesting to note that it is associated with right > left asymmetry of spindle density and power at central electrodes proximal to primary motor cortex (Nishida and Walker, 2007). Sleep spindles are brief, powerful bursts of synchronous neural firing that reach peak density late in the night (De Gennaro et al., 2000) and are hypothesized to mediate the consolidation of procedural memory on the MST (Nishida and Walker, 2007; Rasch et al., 2008; Walker et al., 2002) and other motor tasks (Fogel and Smith, 2006; Tamaki et al., 2008). Studies of schizophrenia show reduced spindle activity (Ferrarelli et al., 2007), and positive relations between Stage 2 spindle density and verbal declarative memory performance (Goder et al., 2008). Here, we expected to replicate our finding of reduced overnight improvement of motor procedural learning in schizophrenia and to correlate it with the duration of S2q4 sleep (Walker et al., 2002), reduced sigma frequency power, which corresponds to sleep spindles, and spindle density during S2q4 sleep, specifically at the right central (C4) electrode, and reduced right > - left sigma asymmetry at central electrodes (C4–C3) during S2q4 sleep (Nishida and Walker, 2007; Rasch et al., 2008; Walker et al., 2005).

2. Methods

2.1. Participants

All participants were screened to exclude substance abuse or dependence within the past six months, diagnosed sleep disorders, or any independent conditions that might affect brain function. Outpatients with schizophrenia ($n = 16$) were recruited from an urban mental health center. Two patients were excluded for failing to type a single correct sequence during training. The remaining 14 patients had all been maintained on stable doses of antipsychotic medications for at least six weeks, 12 on atypicals, one on typicals, and one on both. No patients took anticholinergic medications and ten took diverse adjunctive medications for anxiety, agitation, and/or concurrent mood disturbance. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al., 1997). Clinical status was characterized with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983).

Healthy control participants ($n = 16$) without a history of psychiatric illness were recruited from the community. One control did not complete the study. The 14 schizophrenia and 15 control participants did not differ in age, sex, handedness (modified Edinburgh Handedness Inventory White and Ashton (1976)), or mean parental education (Table 1). Participants gave written informed consent and 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. Remuneration included a bonus based on the number of correct sequences typed on each MST administration.

2.2. Procedures

Experimental design: In the week prior to their stay in the Mallinckrodt General Clinical Research Center (GCRC) at Massachusetts General Hospital, participants met with study staff to complete informed consent, tour the GCRC, and receive a wrist actigraph to wear. Following admission to the GCRC, participants were Trained on the MST and Tested nine hours later (Fig. 1). They were then Trained on a second MST sequence and Tested on this sequence after an additional 9 h. Finally, they were retested on the first sequence. For one sequence, Training and Testing occurred across the day (Wake interval), and for the second sequence, Training and Testing occurred across a night (Sleep interval). The order of the Wake and Sleep intervals and of the two MST sequences were counterbalanced within each group. Participants were monitored to ensure that they did not nap during the day.

Finger Tapping Motor Sequence Test (MST): The MST is described in detail elsewhere (Manoach et al., 2004). In brief, participants pressed four numerically labeled keys on a standard computer keyboard with the fingers of their left hand, repeating a five element tapping sequence (e.g., 4–1–3–2–4) "as quickly and accurately as possible" for 30 s. Throughout the finger tapping trials, the numeric sequence was displayed at the top of the screen. Each session con-

Table 1
Means, standard deviations, and group comparisons of demographic data and rating scale scores. The Phi value is the result of a Fisher's Exact Test.

Participant characteristics	Healthy ($n = 15$)	Schizophrenia ($n = 14$)	t	p
Age	42 ± 6	41 ± 7	0.6	0.54
Sex	11M/4F	11M/3F	Phi = 0.06	0.99
Laterality Score (Handedness)	65 ± 46	60 ± 59	.27	0.79
Parental Education (years)[a]	13 ± 3	13 ± 3	0.25	0.80
Age of Onset		24 ± 6	Average Level of	
Length of Illness (years)		16 ± 8	Severity	
BPRS		18 ± 12	Minimal	
PANSS positive		15 ± 7	Mild	
PANSS negative		15 ± 5	Mild	
SANS		39 ± 17	Mild	

[a] One healthy and two schizophrenia participants were unable to provide this information.