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Spared and impaired sleep-dependent memory consolidation in schizophrenia

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ABSTRACT

Objective: Cognitive deficits in schizophrenia are the strongest predictor of disability and effective treatment is lacking. This reflects our limited mechanistic understanding and consequent lack of treatment targets. In schizophrenia, impaired sleep-dependent memory consolidation correlates with reduced sleep spindle activity, suggesting sleep spindles as a potentially treatable mechanism. In the present study we investigated whether sleep-dependent memory consolidation deficits in schizophrenia are selective.
Methods: Schizophrenia patients and healthy individuals performed three tasks that have been shown to undergo sleep-dependent consolidation: the Word Pair Task (verbal declarative memory), the Visual Discrimination Task (visuoperceptual procedural memory), and the Tone Task (statistical learning). Memory consolidation was tested 24 h later, after a night of sleep.
Results: Compared with controls, schizophrenia patients showed reduced overnight consolidation of word pair learning. In contrast, both groups showed similar significant overnight consolidation of visuoperceptual procedural memory. Neither group showed overnight consolidation of statistical learning.
Conclusion: The present findings extend the known deficits in sleep-dependent memory consolidation in schizophrenia to verbal declarative memory, a core, disabling cognitive deficit. In contrast, visuoperceptual procedural memory was spared. These findings support the hypothesis that sleep-dependent memory consolidation deficits in schizophrenia are selective, possibly limited to tasks that rely on spindles. These findings reinforce the importance of deficient sleep-dependent memory consolidation among the cognitive deficits of schizophrenia and suggest sleep physiology as a potentially treatable mechanism.

1. Introduction

It is now well-established that sleep plays a critical role in memory consolidation – processes that stabilize and enhance recently encoded memories, integrate them into existing associative networks and extract generalities from their content (Stickgold, 2005; Walker and Stickgold, 2010). Recent work in both humans and animal models has demonstrated the importance of specific brain oscillations, including sleep spindles, in the consolidation of different memory types during sleep (Dudai et al., 2015; Rasch and Born, 2013; Stickgold and Walker, 2013). Schizophrenia (SZ) patients show a specific reduction in sleep spindles (for review see Manoach et al., 2016), a thalamocortical oscillation characterizing non-rapid eye movement (NREM) Stage 2 sleep (N2). Sleep spindles correlate with IQ and are thought to both promote long-term potentiation and enhance memory consolidation (Fogel and Smith, 2011). Chronic medicated SZ patients also have reduced sleep-dependent consolidation of motor procedural memory (Genzel et al., 2015; Genzel et al., 2011; Manoach et al., 2010; Manoach et al., 2004; Wamsley et al., 2012) and declarative memory for pictures (Göder et al., 2015), deficits that correlate with reduced spindle activity (Göder et al., 2015; Wamsley et al., 2013; Wamsley et al., 2012). Reduced spindle activity that correlates with cognitive function is also seen in non-psychotic first-degree relatives of SZ patients and early-course antipsychotic drug-naïve SZ patients (Manoach et al., 2014; Schilling et al., 2017) suggesting that the spindle deficit is an endophenotype of SZ (Manoach et al., 2016). The goal of the present

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study was to better define the scope of the sleep-dependent memory deficit in SZ. Findings of dissociations (e.g., reduced sleep-dependent consolidation of motor procedural memory in the context of intact consolidation of memory for a complex figure; Seeck-Hirschner et al., 2010), suggest that only certain memory types are affected. In the present study we tested the hypothesis that deficits in sleep-dependent memory consolidation of memory are selective and present on tasks that have previously been associated with spindles.

A challenge to studying sleep-dependent memory consolidation in SZ is identifying tasks that allow patients to achieve a comparable level of baseline (pre-sleep) performance to controls. This makes it less likely that any observed group differences in sleep-dependent consolidation reflect encoding differences at baseline. The three tasks utilized meet this criterion and have shown sleep-dependent consolidation in healthy adults (i.e., better performance after sleep than after an equivalent interval of daytime wake). We probed declarative memory with a Word Pair Task (WPT) that requires learning of semantically unrelated word pairs. Previous work shows that sleep "protects" newly learned word pairs (i.e., results in reduced forgetting and less susceptibility to interference (Ellenbogen et al., 2006; Payne et al., 2012; Wilson et al., 2012). Sleep-dependent protection of WPT performance correlates with the percentage of NREM Stage 3 sleep (N3) during a daytime nap (Baran et al., 2016), percentage of NREM (N2 plus N3) during nocturnal sleep (Mantua et al., 2015) and with sleep spindles (Gais et al., 2002; Lustenberger et al., 2015; Schabus et al., 2008; Schabus et al., 2004; Schmidt et al., 2006; Studte et al., 2017). Transcranial direct current stimulation that increases time spent in N3, slow oscillations and the number of slow spindles (8-12 Hz) enhances WPT recall (Marshall et al., 2006; Marshall et al., 2004) while transcranial alternate current stimulation disrupting slow wave activity impairs it (Garside et al., 2015).

The visual discrimination task (VDT) measures visuoperceptual procedural memory, requiring participants to determine the arrangement of a target embedded in a background of distractors (Karni et al., 1994). The target screen is presented briefly and is followed, after a variable interstimulus interval (ISI), by a mask screen, allowing determination of a threshold ISI – the minimum ISI required for 80% accuracy. After sleep, the threshold ISI is reduced (Karni et al., 1994; Stickgold et al., 2000a) and this improvement in performance correlates with percent of time in N3 in the first quarter of the night and rapid eye movement (REM) sleep in the last quarter of the night, but is best predicted by the product of these two sleep parameters, suggesting a two-step consolidation process (Stickgold et al., 2000b).

Finally, we investigated sleep-dependent consolidation of statistical learning using the Tone Task (Durrant et al., 2011). Participants hear a probabilistically determined sequence of notes. They are then asked to identify which of two brief sequences sounds similar. Sleep improves the recognition of novel sequences with the same structure presumably by facilitating the abstraction of statistical rules embedded in the sequences. Post-sleep improvement correlates with time in N3 (Durrant et al., 2013; Durrant et al., 2011).

2. Materials and methods

2.1. Participants

Schizophrenia outpatients (n = 28), diagnosed with a Structured Clinical Interview for DSM-IV (SCID; First et al., 1997) and characterized with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) were recruited from an urban mental health center. Two patients were unmedicated, and the rest were maintained on stable doses of antipsychotic medications and adjunctive agents (including antidepressants, benzodiazepines and mood stabilizers; Supplemental Table 1) for at least six weeks.

Healthy controls (n = 32), screened to exclude personal histories of mental illness with a SCID-Non-Patient Edition; (First et al., 2002) or family histories of SZ spectrum disorders or psychosis, were recruited from the community through advertisements.

Potential participants with current diagnoses of sleep disorders, treatment with sleep medications, a history of significant head injury or neurological illness or substance abuse or dependence within the past six months were excluded.

Controls and patients did not differ in age or parental education but there were more males in the schizophrenia group (trend-level difference: $p = 0.06$; Table 1).

The study was approved by the Partners Human Research Committee and participants gave written informed consent. In addition to a base rate of pay, participants received a bonus of $0.05 for each correct response on the memory tasks as an incentive to enhance attention and motivation.

2.2. General procedure

Training and Test sessions were separated by 24 h to avoid circadian effects. Tasks were presented in a fixed order (Fig. 1A) and each session lasted approximately 2 h. At the beginning of each session, participants filled out the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973) to measures alertness. At the end of the Test session, participants completed a questionnaire about sleep duration and quality for the previous night, daytime caffeine use and how well-rested they felt.

2.3. Word-Pair Task (WPT)

Stimuli were 24 semantically unrelated word pairs (Payne et al., 2012). The task consisted of four phases: Initial Exposure, Feedback Training, Pre-Sleep Test and Post-Sleep Test (Fig. 1B). Participants were presented with 24 word pairs and instructed to "remember which words go together." During Initial Exposure, participants studied cue-target word pairs. During Feedback Training, participants were presented with the cue and asked to recall the target; feedback was provided. Pre- and Post-Sleep recall were tested with no feedback.

2.4. Visual discrimination task (VDT)

The VDT (Stickgold et al., 2000a) was adapted for a population with SZ by adding a task demonstration, having subjects report the peripheral target orientation *before* rather than after the letter, and monitoring fixation. Participants were tested in a dark room while resting their head on a chin rest 35-40 cm from the computer screen. Participants completed the task demonstration to preview the trial structure and practice response key mapping. To initiate each trial, participants fixated a white cross in the center of a black screen and after a jittered interval the target screen would appear (Fig. 1C). Fixation was monitored with an eye tracker (EyeLink II, SR Research, Ontario, CA). Target screens contained a rotated "T" or "L" at the center and a horizontal or vertical array of three diagonal bars in the lower-left quadrant. Following the

Table 1
Participant characteristics. Means ± standard deviations and group comparisons of demographic data.

	Schizophrenia (n = 28)	Healthy Controls (n = 32)	t	p
Age (years)	31.6 ± 7.2	31.9 ± 6.3	0.19	0.84
Parental Education (years)	14.4 ± 3.2	14.7 ± 3.3	0.42	0.68
Sex	6F/22 M	15F/17 M	$\chi^2 = 4.41$	0.06
			Average Level of Severity	
PANSS Total	71 ± 13		*Mild*	
PANSS Positive	17 ± 5		*Mild*	
PANSS Negative	19 ± 5		*Mild*	
PANSS General	35 ± 6		*Mild*	

PANNS, Positive and Negative Syndrome Scale (Kay et al., 1987).

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