Effects of daytime naps on procedural and declarative memory in patients with schizophrenia

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ABSTRACT

Sleep has been identified as a state that optimizes the consolidation of newly acquired information in memory. Straight memory deficits and sleep disturbances are well-known in patients with schizophrenia. This study tested the hypothesis that patients with schizophrenia have a deficit in procedural and declarative memory consolidation after a short midday nap when compared to healthy controls and patients with remitted to moderate major depression.

Following a normal night's sleep, 22 healthy subjects, 20 patients with major depression and 21 patients with schizophrenia were studied in a napping and wake condition in a random-order cross-over design, early in the afternoon. To test declarative memory, the Rey–Osterrieth Complex Figure Test respectively the Taylor Complex Figure Test and, for procedural learning, a mirror tracing task were performed.

The present study is the first to demonstrate significant differences between individuals with schizophrenia, depression and healthy matched controls with regard to measures of sleep and memory performance after a short period of daytime sleep (napping). In particular we found that a daytime nap of only about 40 min led to improvement of declarative memory performance in all investigated groups, whereas no beneficial effect was seen on procedural performance in the group of medicated patients with schizophrenia in contrast to healthy controls and patients with remitted to moderate major depression.

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1. Introduction

Today there is little doubt that sleep plays an important role in memory consolidation (Peigneux et al., 2001; Stickgold, 2005). Disturbance or absence of certain sleep stages results in impaired recall of specific memory tasks the following morning. Based on the observations in split-night experiments, it was hypothesized that the consolidation of procedural memory depends on rapid-eye-movement (REM)-sleep, while declarative memory processes depend on non-REM or, more specific, slow-wave sleep (SWS) (Plihal and Born, 1997). However, there is growing evidence that this useful working model might be over-simplified, as e.g. drug-induced REM sleep suppression does not generally interfere with performance in specific motor skill memory (Rasch et al., 2009). Furthermore, other studies have proven the importance of sleep spindles, which occur in non-REM sleep, not only for declarative (Schabus et al., 2004) but also for procedural memory consolidation (Rasch et al., 2009). Hence, REM sleep alone might not be as important for sleep-related memory consolidation as initially conceived. Instead, both REM sleep and non-REM sleep might be necessary for memory processes in general and might be involved in complementary fashion (Stickgold, 2005).

Disturbed sleep can be found in most patients with schizophrenia. Measured by polysomnography, alterations in Stage 2 sleep, SWS and REM sleep variables, as well as increased sleep latency, are common in, but not necessarily specific to schizophrenia as they also appear in major depression and other psychiatric disorders (Chouinard et al., 2004; Göder et al., 2004; Monti and Monti, 2005; Poulin et al., 2003). A specific observation was made by Ferrarelli and colleagues (2007), who demonstrated reduced sleep spindle activity in patients with schizophrenia. Sleep spindles are generated by the thalamic reticular nucleus and are modulated by corticothalamic and thalamocortical connections. It has thus been speculated that spindles indicate the repeated activation of thalamocortical or hippocampocortical networks that are suggested as the basis for reorganization and consolidation of memory by inducing synaptic plasticity (Schabus et al., 2004, 2006).

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The connection between sleep and memory performance in patients with schizophrenia and major depression have been described in several studies (Göder et al., 2004, 2007, 2008). However, despite distinct sleep disturbances, patients with major depression have clearly less cognitive deficits when compared to patients with schizophrenia. Our previous sleep studies in patients with schizophrenia showed positive associations between the length of slow-wave sleep and declarative memory consolidation during sleep (Göder et al., 2004, 2008). For healthy subjects there is solid evidence that apart from the positive effects of nocturnal sleep on memory performance, diurnal sleep periods (naps) also have beneficial effects (Mednick et al., 2003; Backhaus and Junghanns, 2006; Tucker et al., 2006 and Lahl et al., 2008).

Based on the observation of Manoach et al. (2004) that sleep-dependent consolidation of procedural memory is absent in patients with schizophrenia in nocturnal sleep, in the present study we aimed to examine the effect of a short midday sleep phase on procedural and declarative memory consolidation in patients with schizophrenia compared to depressed patients and healthy controls. Our working hypothesis was that a period of midday sleep should result in an increase of performance in the mirror tracing test in healthy and depressed subjects, but not in patients with schizophrenia.

2. Methods

2.1. Subjects

The study was approved by the local Ethics Committee and was carried out according to the Declaration of Helsinki and conducted from May 2007 to March 2008. All subjects gave their informed written consent. Seventy five subjects were recruited: 25 inpatients with schizophrenia, 25 inpatients with major depression and 25 healthy controls, matched for age and education. Twelve subjects (four with schizophrenia, five with depression and three controls) had to be excluded from the data analysis because they were unable to sleep for 15 min or more in the napping condition. Of the remaining 63 subjects, 21 had been diagnosed with schizophrenia (six females), 20 patients with major depression (12 females) and 22 were healthy subjects (13 females; detailed demographic parameters are shown in *Supplementary* Table 1 online). A senior psychiatrist interviewed all the participants to obtain a complete psychiatric and medical history and to confirm the psychiatric diagnosis based on ICD-10 criteria. A physical examination was performed, and in particular, neurological, movement, endocrinological and sleep disorders were excluded. Clinical state was characterized for the patients with schizophrenia using the "Positive and Negative Syndrome Scale" (PANSS) and for the patients with major depression using the "Beck Depression Inventory" (BDI) and the 21-item "Hamilton Depression Rating Scale (HDRS)".

All participants with schizophrenia were diagnosed as paranoid subtype (ICD-10 F20.0). Of the 21 patients with schizophrenia, 20 received atypical antipsychotic medication (amisulpride, risperidone, olanzapine, clozapine or quetiapine) and one patient received haloperidol as a typical antipsychotic drug. Five patients were additionally treated with promethazine ($n = 1$), biperidin ($n = 3$) and lamotrigine or carbamazepine ($n = 2$). All were inpatients with a mean disease duration of 8.4 (SD = 6.6) years.

The depressed inpatients were confirmed to have a history of current major depression (ICD-10 F32.1; F32.2; F33.1; F33.2), without evidence of past or current psychotic symptoms. Current symptoms were rated by HDRS. The patients were on stable medication with selective serotonin re-uptake inhibitors ($n = 8$), norepinephrine re-uptake inhibitor ($n = 3$), mirtazapine ($n = 1$) or received a treatment with two antidepressants ($n = 8$). At the time of the recording, three subjects were in remission (HDRS $\leqslant 7$) and 17 had mild to moderate depression (HDRS = 8–19).

Healthy control subjects with no history of psychiatric or sleep-related disorders were recruited through advertisements. The control subjects did not take psychoactive medication or illegal drugs and reported regular sleep/wake schedules.

Subjects from all groups were free of any GABA-(A)-receptor agonists including benzodiazepine for a wash-out period of at least 14 days prior to experiments. The medication was stable for both conditions. Each subject underwent a careful clinical evaluation to exclude accompanying severe somatic, neurological or endocrinological disorders or substance abuse. The subjects were instructed not to rise earlier than 05.30 h or later than 08.00 h on experimental days of study. No alcoholic drinks or caffeinated beverages were allowed the night before and on the morning of the experiments.

2.2. Study design

All participants of each group were randomly assigned to begin with the napping or wake condition. Both napping and wake conditions were scheduled between 1:00 and 2:30 p.m., and monitored with polysomnography and video recording. For the wake condition, subjects were allowed to engage in activities with low physical effort, e.g. reading or watching movies under supervision. Immediately before (t1) and approximately 30–40 min after (t2) nap or wake condition, respectively, the subjects were submitted to declarative and procedural memory tasks.

2.3. Measures of sleep

Polysomnography was recorded employing standard procedures, and the following parameters were measured: electroencephalographic activity (EEG: C3-A2, C4-A1 according to the 10–20 system), electro-occulographic activity (EOG) and submental electromyographic activity (EMG). Recordings were visually scored according to standard criteria by a trained rater under blind conditions (Rechtschaffen and Kales, 1968). For sleep spindle detection, a bandpass filtered signal of the raw EEG was used. The bandpass filter only allowed frequencies within the range of 12–16 Hz. All spindles were visually identified in all epochs scored as Stage 2 sleep. The following parameters were computed: total sleep time (TST), sleep onset latency (SOL), Stage 2 sleep, REM sleep, slow-wave sleep (SWS) and Stage 2 sleep spindle density.

2.4. Memory tasks

Declarative memory was assessed by the non-verbal Rey–Osterrieth Complex Figure Test (ROCF; Osterrieth, 1944), respectively the Taylor Complex Figure Test in a counterbalanced manner (Hubley and Jassal, 2006). In these tests the subject is requested first to copy a complex figure. After the nap, subjects were disconnected from the EEG recording and allowed a short break (minimum of 30 and maximum of 40 min after waking up) before they were instructed to redraw the figure from memory (announced recall).

To test procedural memory we used the mirror tracing skill task. In this task, subjects had to draw between the doubled lines of geometric figures. The direct visual access to the platform with the figures was prevented by a 30 by 22 cm board and the figures could only been seen via a 26 by 18 cm mirror. All subjects used a 0.5 mm ballpoint pen and were instructed to work as fast and as accurately as possible. Before learning the actual figure (star before (t1) and after (t2) nap/wake condition) subjects trained a simple triangle figure until they could draw it with less than 12 errors (Gais et al., 2006, adapted to psychiatric patients). We assessed