Impaired Sleep-Related Memory Consolidation in Primary Insomnia—A Pilot Study

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Study Objectives: To compare sleep-related consolidation of procedural memory in patients with primary insomnia and healthy controls.

Design: Controlled comparison pilot study

Setting: Sleep Laboratory of the Department of Psychiatry and Psychotherapy, University of Freiburg, Germany.

Patients or Participants: Seven patients with primary insomnia and 7 sex-, age-, and IQ-matched healthy controls.

Interventions: Subjects spent 1 night in the sleep laboratory with polysomnographic monitoring. Performance on a mirror tracing task was measured before and after sleep.

Measurements and Results: Polysomnography revealed a trend toward disturbed sleep in the patients, compared with the control group, without reaching significance. Performance in the mirror tracing task before sleep did not differ between the groups. Both groups performed significantly better in the retest condition after sleep. Healthy controls showed an improvement of 42.8% ± 5.8% in the mirror tracing draw time, whereas patients with insomnia showed an improvement of 20.4% ± 14.8% (multivariate analyses of variance test session × group interaction: F3,10 = 10.9, p = .002).

Conclusions: These preliminary findings support the view that sleep-associated consolidation of procedural memories may be impaired in patients with primary insomnia.

Keywords: Primary insomnia, sleep, memory consolidation

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INTRODUCTION

A MOUNTING BODY OF EVIDENCE INDICATES THAT SLEEP CAN CONTRIBUTE TO THE CONSOLIDATION OF NEWLY ENCODED MEMORY TRACES.1 Early studies in humans proposed that rapid eye movement (REM) sleep may primarily improve procedural learning, whereas non-REM sleep may predominantly facilitate the consolidation of declarative memories.2 Recent studies have not consistently supported this “dual-process hypothesis” but have postulated that different sleep stages consolidate memory traces in a complementary sequential manner.3-5 This “sequential hypothesis” is supported by studies demonstrating that a sequence of initial slow-wave sleep (SWS) and subsequent REM sleep provides favorable conditions for the consolidation of memories, such as those required for the improvement in a texture-discrimination task.6

Other studies have begun to assess possible neural underpinnings of the behavioral association between sleep and memory. Wilson and McNaughton7 demonstrated in rats that activity patterns of hippocampal “place cells” recorded during training in a spatial-orientation task were replayed during subsequent periods of sleep. In humans, patterns of brain activity measured during performance of a serial reaction time task were found to be reactivated during subsequent REM sleep.8 These and other findings9 suggest that newly acquired memories are processed during sleep and that this process may contribute to neuropsychological changes10 believed to ultimately underlay long-term memory formation.11 Patients with primary insomnia report complaints in various cognitive domains, including attention and memory.12-14 Neuropsychological assessments administered in the daytime have largely failed to confirm these subjective deficits.12,13 However, sleep-related memory consolidation that may relate to the complaints of subjects with poor sleep has not been systematically investigated. Here, we present preliminary data from a study designed to test the hypothesis that patients with primary insomnia may demonstrate an impairment of sleep-associated memory consolidation. A procedural mirror tracing task was used because consolidation in this task has been shown to be facilitated during sleep.2 The assessment of sleep-related memory processing in primary insomnia may lead to a better understanding of cognitive aspects of this important and prevalent sleep disorder.

METHODS

Subjects

Seven patients with primary insomnia and 7 healthy controls were studied (Table 1). To ensure a representative sample, patients with insomnia scheduled for a sleep laboratory assessment as part of their clinical evaluation were invited to participate in the study. Insomnia subjects met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for primary insomnia,15 as assessed by a clinical interview and a sleep diary that was filled out for 2 weeks prior to the study. The mean ± standard deviation duration of illness was 3.5 ± 2.4 years, range 2 to 30 years. One patient reported difficulties primarily falling asleep, 2 patients reported difficulties primarily staying asleep, and 4 patients reported a combination of early, middle, or late sleep disturbances. Six of the patients had taken medications for their sleep disturbances at least one point in time, and 3 had experiences with behavior or cognitive behavior therapies. Healthy control subjects matched...
for sex, age and full-scale IQ were recruited from the community. Their good-sleeper status was ensured by clinical interviews and sleep diaries for 2 weeks. All participants underwent an extensive examination to rule out any comorbid physical or psychiatric disorder. All participants were free of any medication for at least 2 weeks prior to the onset of the study and did not consume alcohol or caffeine during the study. All subjects were right handed and nonsmokers. A urine drug screening after the first night in the sleep laboratory demonstrated that all participants were free of any benzodiazepines, barbiturates, amphetamines, or opiates. Sleep diaries for 2 weeks ensured that the subjects’ usual sleep times approximated the imposed sleep schedule in the laboratory. All participants were informed in detail and provided their written consent prior to the onset of the study. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethic committee.

**Experimental Design**

All participants slept 1 night in the sleep laboratory with polysomnography derived from 10:30 PM to 6:30 AM. A mirror tracing task was performed at 8:30 to 9:00 PM prior to sleep and at 7:00 to 7:30 AM after sleep. The German version of the Pittsburgh Sleep Quality Index was used to assess subjective sleep quality and disturbances over a 2-week time interval. The Schlafrfragebogen-A is a self-rated questionnaire that assesses sleep quality of the preceding night and was administered in the morning after the experimental night.

**Mirror Tracing Task**

The mirror tracing procedures in the present study, including the line-drawn stimuli, followed closely the procedures outlined by Plihal and Born. The task was chosen because it is an established task for procedural learning and improvement in the task has been shown to be enhanced by sleep. Participants were asked to trace different line-drawn stimuli using a stylus with an electronic light sensor that measures (1) draw time, (2) number of errors, and (3) total error time. Errors refer to events when the stylus left the trace. Subjects were asked to work as quickly and accurately as possible. Visual access to the stimuli was provided only indirectly via a mirror. During the learning condition in the evening, mirror tracing a star was repeated until the participant reached a criterion of 15 or fewer errors. After this training condition, 6 line-drawn figures were presented, 1 after the other. During the retest condition in the following morning, subjects were asked to mirror trace the star 1 single time to keep conditions comparable. Then, the 6 figures of the preceding evening were presented. Learning performance was assessed by measuring the number of trials to criterion for mirror tracing the star and measuring (1) the mean draw time, (2) the mean total error count, and (3) the mean error time for mirror tracing the 6 figures. During the retest session in the following morning, the same measures were assessed for tracing the 6 figures. Additionally, the percentage of improvement in draw time from the evening to the morning condition was calculated.

**Sleep Recordings**

Sleep recordings were performed from 10:30 PM to 6:30 AM and scored according to standard criteria by experienced raters who were blind to the clinical condition of the subjects. All raters participate in weekly meetings discussing and solving scoring problems. Interrater reliability for all technicians involved in scoring polysomnograms is checked bimonthly. Coefficients of agreement between 2 raters are required to be higher than 85%. The following variables of sleep continuity and architecture were assessed: sleep-onset latency, defined as the period between when the lights were turned out and the first 30-second epoch of stage 2 sleep (sleep latency); sleep period time, defined as the period between sleep onset and the final awakening; sleep efficiency, defined as the ratio of total sleep time to time in bed × 100%; and time spent in waking and in sleep stages 1, 2, slow-wave sleep (combined stages 3 and 4) and REM sleep, as a percentage of the sleep period time. REM sleep latency was defined as the period between sleep onset and the occurrence of the first 30-second epoch of REM sleep, including intermittent waking times (REM latency). REM density was calculated as the ratio of 3-second miniepochs of REM sleep containing rapid eye movements to the total number of 3-second miniepochs of REM sleep * 100%.

**Data Analysis**

Descriptive presentation of the data includes mean values and standard deviations. Nonparametric Mann-Whitney tests were used for group comparisons of demographic characteristics, sleep variables, the number of trials to criterion (star), and the percentage of improvement in draw time between insomnia patients and controls. To quantify the difference between groups, Cohen effect sizes for sleep variables were calculated as the differences between the 2 means, divided by the pooled estimates of standard deviation. A 2-factor multivariate analyses of variance with factors for repeated

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Table 1—Study Subjects

<table>
<thead>
<tr>
<th>Healthy Controls</th>
<th>Insomnia Patients</th>
<th>Z</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/ women</td>
<td>3/4</td>
<td>3/4</td>
<td>—</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.9 ± 4.1</td>
<td>44.3 ± 5.3</td>
<td>-0.51</td>
</tr>
<tr>
<td>Age range, y</td>
<td>41-51</td>
<td>40-54</td>
<td>—</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>100.7 ± 14.3</td>
<td>101.6 ± 18.4</td>
<td>-0.06</td>
</tr>
<tr>
<td>Years in school</td>
<td>12.0 ± 1.3</td>
<td>10.6 ± 1.7</td>
<td>-1.75</td>
</tr>
<tr>
<td>Subjective memory</td>
<td>59.0 ± 28.0</td>
<td>49.6 ± 9.7</td>
<td>-1.34</td>
</tr>
<tr>
<td>PSQI</td>
<td>3.4 ± 1.8</td>
<td>11.3 ± 3.0</td>
<td>-2.95</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Subjective memory is the subjective memory capacity over the last 4 weeks, as assessed by a visual analogue scale from 0 (poor) to 100 (excellent). PSQI refers to the Pittsburgh Sleep Quality Index. Nonparametric Mann-Whitney tests.

*Significant effect.
measurement (learning and retest session) and group (insomnia patients and healthy controls) was used to test for differences in mirror tracing. Univariate tests are Greenhouse-Geisser corrected. To test potential associations between sleep and memory variables, nonparametric Spearman ρ correlation coefficients were calculated. The level of significance was set at p value < .05 (2-tailed).

RESULTS

Sleep

Results from the sleep recordings are summarized in Table 2. Repeated Mann-Whitney tests did not reveal significant differences between insomnia patients and healthy controls. Medium to large effect sizes for sleep efficiency and for the percentage of the sleep period time spent in wake, stage 2 sleep, and REM sleep suggest that significant group differences might have been detected in a larger sample.

Mirror Tracing

In the learning session, the number of trials to criterion (star) did not differ between insomnia patients (3.7 ± 2.4) and healthy controls (3.0 ± 2.1, Mann-Whitney Z = -0.33, p = .742). Table 3 summarizes the subjects’ mean performance data on the mirror tracing task (figures) during the learning and retest sessions. Multivariate testing (Wilks λ) demonstrated a highly significant effect for the factor test session (F_{3,10} = 31.8, p < .001) and test session × group interaction (F_{3,10} = 10.9, p = .002) but not for the factor group (F_{3,10} = 2.3, p = .139). As listed in Table 3, univariate tests indicated a highly significant improvement in all 3 outcome measures of the task for the repeated-measurement factor. Univariate comparison of both groups showed a significant effect for error count that was predominantly driven by a higher error count in the control group, compared with the insomnia patients, in the evening (posthoc contrast: p = .051). Insomnia patients demonstrated a significantly smaller improvement in the parameter draw time from before to after sleep, compared with healthy controls (test session × group interaction). Single values of draw time in the evening and morning conditions for both groups are shown in Figure 1. The significantly lower percentage of improvement of draw time in insomnia patients (20.4% ± 14.8%), compared with healthy controls (42.8% ± 5.8%), is depicted in Figure 2 (Mann-Whitney Z = -2.62, p = .009).

Table 2—Polysomnographic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Insomnia Patients</th>
<th>Z</th>
<th>p value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency, min</td>
<td>27.4 ± 12.3</td>
<td>34.1 ± 44.2</td>
<td>-0.70</td>
<td>.482</td>
<td>-0.21</td>
</tr>
<tr>
<td>Sleep period time, min</td>
<td>449.2 ± 8.8</td>
<td>438.1 ± 47.7</td>
<td>-0.83</td>
<td>.406</td>
<td>0.32</td>
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<tr>
<td>Sleep efficiency, %</td>
<td>78.5 ± 6.5</td>
<td>70.0 ± 19.6</td>
<td>-0.58</td>
<td>.565</td>
<td>0.58</td>
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<tr>
<td>REM latency, min</td>
<td>114.2 ± 56.7</td>
<td>134.3 ± 75.4</td>
<td>-0.70</td>
<td>.482</td>
<td>-0.30</td>
</tr>
<tr>
<td>REM density, %</td>
<td>28.0 ± 6.5</td>
<td>27.8 ± 16.8</td>
<td>-0.96</td>
<td>.338</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Nonparametric Mann-Whitney tests. REM refers to rapid eye movement sleep; SWS, slow-wave sleep.
Correlation Between Sleep Parameters and Improvement in Mirror Tracing

Nonparametric correlations between polysomnographic and subjective sleep parameters and the percentage of improvement in the mirror tracing time are listed in Table 4. The correlations between the listed sleep parameters and the 2 other outcome measures of the mirror tracing task, improvement in error count and error time, did not reach significance and are not listed. With regard to polysomnography, a negative across-group correlation between sleep period time and percentage of improvement in the mirror tracing time was observed. Note that the sleep period time is defined as the period between sleep onset and the final awakening and includes waking and stage 1 sleep. Furthermore, REM density was positively correlated with the percentage of improvement in the mirror tracing time across the groups. With regard to subjective parameters, a negative across-group correlation between the Pittsburgh Sleep Quality Index and the percentage of improvement in mirror tracing time and a highly positive correlation between the subjective sleep quality of the experimental night (Schlaffragebogen-A) and the improvement in the task was observed. No significant correlations were observed in the within-group correlations. It is important to note that the given correlations are not corrected for multiple testing and have only exploratory but not confirmative value.

DISCUSSION

These preliminary data support our initial hypothesis that the sleep-related consolidation of procedural memory traces may be impaired in patients with primary insomnia. Evidence for this is that the percentage of improvement in draw time from before to after sleep in a mirror tracing task was significantly lower in patients with insomnia, compared with sex-, age-, and IQ-matched healthy controls (Figures 1 and 2). Polysomnographic comparison revealed a trend toward a disturbed sleep profile in the insomnia group, in comparison with the control group, but the trend did not reach significance. Prior to concluding that sleep-related memory consolidation may be disturbed in primary insomnia, a number of limitations need to be addressed.

The presented results are preliminary in nature. The number of subjects was small, and the findings require replication in a larger sample. The study design was based on substantive evidence indicating that sleep facilitates the consolidation of procedural memories. However, waking control conditions that include morning-to-evening and nightly sleep-deprivation periods would be necessary to provide direct evidence that the observed differences in improvement from before to after sleep are distinctly sleep-related. Additionally, the number of years in school was markedly, although not significantly, higher in healthy controls. This higher level of education may have contributed to a better improvement in healthy controls. The similarity of full-scale IQ values in both groups, however, suggests that the general capability of cognitive performance was similar in both groups and is not sufficient to explain the results.

The present data are based on a single experimental night, without preceding adaptation to the sleep laboratory condition. This design may have contributed to the relatively poor sleep in the control group (Table 2), since a particularly disturbed sleep profile in the first night of sleep in the laboratory has been described as a “first-night effect” in healthy subjects. The differences in polysomnographic parameters may have been further reduced by a “reversed first-night effect,” characterized by better sleep in a first compared with a second night of sleep in the laboratory that has been observed in patients with insomnia. Following this line of arguments, the differences between healthy and insomnia subjects in the present study may be even more pronounced in a second or subsequent sleep-laboratory nights. Note that patients with insomnia made significantly fewer errors during mirror tracing (Table 3, group main effect for error count, posthoc contrasts for single test sessions not significant). It would be informative to further assess whether patients with insomnia differ from good sleepers in terms of accuracy or perfectionism, which might represent a predisposition for the development of insomnia, a conse-

Table 3—Mirror Tracing Task

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th></th>
<th></th>
<th>Insomnia</th>
<th></th>
<th></th>
<th>Test session</th>
<th>Group</th>
<th>Session × Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evening</td>
<td>Morning</td>
<td></td>
<td>Evening</td>
<td>Morning</td>
<td></td>
<td>F, L,2</td>
<td>p</td>
<td>F, L,2</td>
</tr>
<tr>
<td>Time, sec</td>
<td>117.4 ± 34.7</td>
<td>67.0 ± 19.6</td>
<td></td>
<td>100.0 ± 41.6</td>
<td>76.1 ± 24.8</td>
<td></td>
<td>47.6</td>
<td>.000*</td>
<td>0.7</td>
</tr>
<tr>
<td>Error count, no.</td>
<td>18.5 ± 11.6</td>
<td>5.6 ± 4.7</td>
<td></td>
<td>7.4 ± 6.2</td>
<td>3.3 ± 2.4</td>
<td></td>
<td>14.9</td>
<td>.002*</td>
<td>4.8</td>
</tr>
<tr>
<td>Error time, sec</td>
<td>8.7 ± 7.7</td>
<td>4.1 ± 6.2</td>
<td></td>
<td>6.9 ± 6.5</td>
<td>1.9 ± 1.5</td>
<td></td>
<td>12.3</td>
<td>.004*</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. Multivariate analyses of variance with factors Test Session and Group. Univariate tests are Greenhouse-Geisser corrected.
*Significant effect.

Figure 2—Improvement in mirror tracing task draw time, expressed as the percentage of improvement from draw time in the evening prior to sleep to draw time in the morning after sleep, Mann-Whitney test. Z = -2.62, p = .009.
the alternation between distinct sleep stages, consolidation may relate to a multistep process characterized by correlations were not corrected for multiple testing and should be final awakening and includes various periods of waking, stage 1 this parameter is defined as the period between sleep onset and the period time and memory performance is less informative, since the previous finding that procedural memories are enhanced by sleep periods rich in REM sleep. The present across-group correlation between REM density (Table 4) suggests that neural processes related to the generation of REMs may facilitate the consolidation of newly acquired traces of procedural memories. This observation is indirectly in line with the previous finding that procedural memories are enhanced by sleep periods rich in REM sleep.3 The correlation between sleep period time and memory performance is less informative, since this parameter is defined as the period between sleep onset and the final awakening and includes various periods of waking, stage 1 sleep, and other sleep stages. It is important to note that the given correlations were not corrected for multiple testing and should be seen only as exploratory. Furthermore, sleep-associated memory consolidation may relate to a multistep process characterized by the alternation between distinct sleep stages,3-6 which can not be assessed by simple correlational analyses.

Interestingly, sleep-related improvement in the mirror tracing task clearly differed between patients with insomnia and healthy controls, but sleep parameters did not. The lack of polysomnographic differences may represent a false negative finding in the context of insufficient power, as indicated by the, in part, high effect sizes (Table 2). In addition, another perspective is worth noting. A dissociation between the polysomnographic and behavioral level may be, in part, explained by recent positron emission tomography studies demonstrating a significantly altered brain metabolism in patients with primary insomnia, even in periods of polysomnographically undisturbed sleep.22 This suggests that neural processes beyond the level of polysomnography may contribute to behavioral alterations, including subjectively determined nonrestorative sleep or impaired sleep-related memory processing. The high correlations between subjective sleep parameters and procedural memory consolidation in the present study (Table 4) may point in this direction. However, these correlations should be interpreted with caution because they may represent a spurious result driven by the group differences between patients with insomnia and good sleepers.

In conclusion, the present data suggest that sleep-related consolidation of procedural memories may be impaired in patients with primary insomnia. Clearly, these preliminary findings require further studies in adequate sample sizes. A control waking condition should be used to confirm that the findings are distinctly sleep related, and other types of memory should be assessed.

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