Impaired Declarative Memory Consolidation During Sleep in Patients With Primary Insomnia: Influence of Sleep Architecture and Nocturnal Cortisol Release

Jutta Backhaus, Klaus Junghanns, Jan Born, Kornelia Hohaus, Frauke Faasch, and Fritz Hohagen

Background: *A central cognitive function of sleep is to consolidate newly acquired memories for long-term storage. Here, we investigated whether the overnight consolidation of declarative memory in patients with chronic sleep disturbances is impaired, owing to less slow wave sleep (SWS) and an increased cortisol release.*

Methods: *Polysomnographic recordings, serum cortisol concentrations, and overnight memory consolidation in 16 patients with primary insomnia were compared with those of 13 healthy control subjects.*

Results: *Patients displayed distinctly less overnight consolidation of declarative memory ($p < .05$), which was significantly correlated with SWS in the control subjects ($r = .69$) but with rapid eye movement (REM) sleep in the patients ($r = .56$), who had a diminished amount of SWS ($p < .05$). Increased cortisol levels in the middle of the night were associated with impaired retrieval of declarative memory after sleep for both control subjects ($r = -.52$) and patients ($r = -.46$).*

Conclusions: *Primary insomnia is associated with a diminished sleep-related consolidation of declarative memory. Efficient overnight consolidation of declarative memory is associated with high amounts of SWS and low serum cortisol levels during the early part of the night. Where SWS is decreased, REM sleep might play a partly compensatory role in the consolidation of declarative memory.*

Key Words: Sleep, primary insomnia, memory consolidation, declarative memory, cortisol

A number of recent studies provide compelling evidence that sleep plays an essential role in the consolidation of memory (for review see Ficca and Salzarulo 2004; Gais and Born 2004a; Maquet 2001; Peigneux et al 2001; Rauchs et al 2005; Smith 2001; Stickgold et al 2001; Walker and Stickgold 2004). Thus, sleep after a learning period enhances both procedural memories for skills (e.g., Fischer et al 2002; Kuriyama et al 2004; Plihal and Born 1997; Smith and MacNeill 1994; Walker et al 2002, 2003, 2005) and declarative memories (i.e., for episodes and facts) (Gais and Born 2004a). Previous studies provide evidence that nightly declarative memory consolidation benefits primarily from periods of early nocturnal sleep, during which slow wave sleep (SWS) is predominant (Plihal and Born 1997, 1999a; Yaroush et al 1971).

Cortisol modulates hippocampus-dependent declarative memory functions (see, for example, de Quervain et al 2000; Kirschbaum et al 1996; Lupien et al 1997; Newcomer et al 1999; for review, see Het et al 2005). Intravenous infusion of small doses of cortisol during SWS-rich early nocturnal sleep, when the endogenous cortisol release is usually at a minimum, completely blocked any consolidation of declarative memory during sleep (Plihal and Born 1999). An effective inhibition of the glucocorticoid feedback on hippocampal networks seems to be a prerequisite for sleep-associated consolidation of declarative memory (Plihal et al 1999).

Because sleep is important for the consolidation of memory, disturbed sleep should consequently result in its impairment. Primary insomnia is a suitable model to investigate such consequences of disturbed sleep, because this disorder is characterized by a reduced amount of SWS as well as by an increased amount of stage 1 sleep and nocturnal wake time (meta-analyses by Benca et al 1992; Hudson et al 1992). Notably, according to the criteria of DSM-IV (American Psychiatric Association 1994) primary insomnia is not associated with other psychiatric disorders. Thus, it enables the investigation of the consequences of sleep disturbances for memory consolidation without any interference from other psychiatric disorders, such as depression, that might influence memory consolidation.

Patients with primary insomnia perceive their lives as more stressful and experience more pre-sleep arousal than do good sleepers (Morin et al 2003). Neuroendocrinological studies indicate a disinhibited activity of the hypothalamo-pituitary-adrenocortical stress system in these patients, particularly in the evening and early night (Rodenbeck et al 2002; Vgontzas et al 2001), although this was not consistently found (Riemann et al 2002). In an earlier study, we demonstrated a significant decrease of awakening salivary cortisol in primary insomnia patients that was correlated with sleep disturbances and probably associated with enhanced cortisol secretion during the preceding night (Backhaus et al 2004).

The examination of memory functions in these patients yielded mixed results (for an overview see Sateia et al 2000). For the most part, no differences or else only slight ones were found between patients with primary insomnia and healthy control subjects. However, in all these studies with insomnia patients, the encoding and the recall of material were tested on the same day; to our knowledge, none examined the effects of overnight-sleep on the consolidation of newly acquired material.

Given the decrease in SWS, accompanied by a disinhibited release of cortisol during the early night in primary insomnia patients, we hypothesized that these patients would display a specific impairment of the sleep-dependent consolidation of memories. There ought to be pronounced impairment of declarative memory consolidation, which was found in some previous studies to depend particularly on SWS (Gais and Born 2004a, 2004b; Molle et al 2004; Peigneux et al 2004; Plihal and Born 1997, 1999a; Yaroush et al 1971) and which relies, in addition, upon low serum cortisol concentrations (Plihal and Born 1999b), especially during the first half of the night.

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Received August 25, 2005; revised February 20, 2006; accepted March 22, 2006.

0006-3223/06/$32.00
doi:10.1016/j.biopsych.2006.03.051

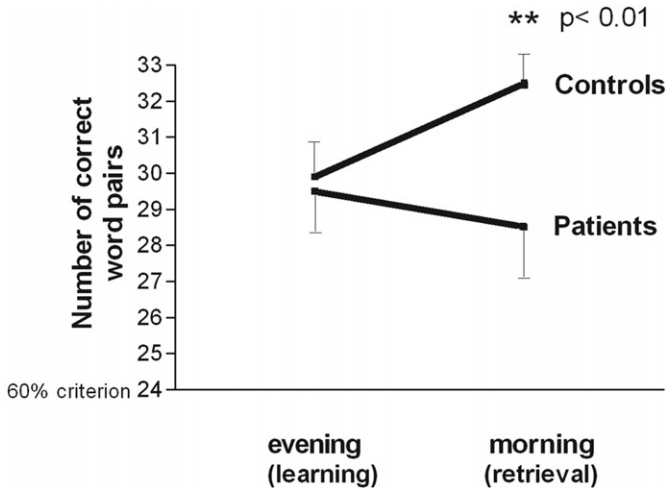

Figure 1. Overnight declarative memory consolidation: number of correctly recalled words on the word-pair associates task at learning (in the evening before retention sleep) and at delayed retrieval testing (in the morning after retention sleep) (means ± SEM).

Methods and Materials

Subjects

Sixteen patients with primary insomnia (8 men) and 13 age-matched healthy control subjects (5 men) participated in the study. Patients were consecutively recruited from the Outpatient Sleep Disorders Clinic of the University of Luebeck, and control subjects were recruited by advertisement. All patients who met the criteria for primary insomnia according to the DSM-IV were asked to participate in the study. The DSM-IV criteria for primary insomnia are sleep disturbances that cause patients to feel consequences like tiredness during the daytime. Furthermore, to fulfill the criteria for primary insomnia according to DSM-IV, patients must not have any other current psychiatric disorder. Other than the primary insomnia in the patients, neither patients nor control subjects had a current psychiatric disorder according to DSM-IV Axis I and Axis II. Moreover, any somatic disorder that might affect sleep also was ruled out in both groups. Patients and control subjects underwent a thorough physical and psychiatric assessment, including the Structured Clinical Interview for the Diagnosis of Psychiatric Disorders according to DSM-IV (SCID), and a battery of routine clinical tests encompassing electrocardiography, electroencephalography, assay of thyroid hormones, blood cell count, and urine analysis. Female participants took part within the first 9 days of their menstrual cycle. Estrogen, as well as progesterone, was measured to confirm the cycle phase. All subjects had a regular sleep-wake rhythm and none were shift workers. They did not take any psychoactive drugs or medications that might affect sleep, and all had a body mass index within the normal range.

The study was approved by the local ethics committee and was conducted according to the Declaration of Helsinki. After a complete description of the study to the subjects, their written informed consent was obtained.

Procedure and Tasks

Each subject spent two nights in the sleep laboratory. The first night served to adapt the subjects to the experimental sleep conditions and to exclude sleep apnea and periodic leg movements. On the afternoon of day 2, an indwelling catheter was inserted into an antecubital vein to draw blood for assessment of cortisol every 15 min during bedtime. All subjects had 8 hours of bedtime beginning between 10:00 PM and 11:00 PM, adapted to their regular bedtime at home. Before bedtime, subjects learned a declarative and a procedural memory task.

The declarative memory task was a word-pair associates task consisting of 40 word pairs of German nouns that were standardized with respect to word frequency, length, emotionality, meaningfulness, and concreteness (Plihal and Born 1997). Two additional word pairs at the beginning and again at the end of the test served to buffer primacy and recency effects and were not included in the analysis. Each word pair was presented visually for 5 sec. Immediately after presentation of all word pairs, the subjects were to recall orally the second word upon presentation of the first (cued recall). The list was presented repeatedly in different order until the subject had correctly recalled at least 24 words (60% criterion).

To test procedural memory, a mirror-tracing task was used (Plihal and Born 1997). The subject had to move an electronic stylus as fast and as accurately as possible along the black line of a figure that they could see only through a mirror. Subjects first traced repeatedly a star-like figure until they had reached a criterion of fewer than six errors (deviating from the black line) per run. Thereafter, they were to trace six different figures, for which the average drawing time per figure (total time), the number of errors (error count), and the error time (time spent off the black line) were calculated.

The following morning, retrieval of the word-pair associates task and the mirror-tracing task was tested: Subjects were asked to again recall orally the second word in a pair upon presentation of the first (cued recall). Upon completion of this task, they then repeated the mirror-tracing of the six test figures. Memory testing began 15 min after awakening in order to avoid any impairing effects of sleep inertia. After retrieval testing on the declarative and procedural memory tasks, subjects underwent an extensive standardized test battery to control for effects of alertness and vigilance (Zimmermann and Fimm 1993). This test battery consisted of the following tasks: an alertness task tested simple reaction time to visual stimuli, some of which were presented with a preceding auditory signal; a "Go/No Go" task demanded reactions to two of five visual stimuli, thus testing the subjects' ability to suppress reactions to irrelevant stimuli; a simple reaction task and a complex reaction task measured the ability to change the focus of attention between alternating stimuli of relevance; and a task assessed their ability to maintain vigilance to relevant stimuli occurring with low probability among frequently presented standard stimuli.

Polysomnographic Recordings and Sleep Questionnaire

Electroencephalogram (EEG) electrodes were positioned at C3 referenced against A2 and at C4 referenced against A1 as defined by

Table 1. Non-Declarative Memory Task (mirror-tracing) (means ± SD)

	Controls (n = 13)	Patients (n = 12)	z	Mann–Whitney U Test p
Total Time (in sec)				
Learning	111.2 ± 53.9	104.5 ± 32.2	−.11	.94
Retrieval	83.1 ± 40.4	70.6 ± 17.8	−.71	.50
Error Count				
Learning	19.1 ± 16.4	12.9 ± 10.0	−.65	.54
Retrieval	8.6 ± 9.7	5.0 ± 3.1	−.41	.69
Error Time (in sec)				
Learning	9.1 ± 9.3	6.8 ± 5.6	−.33	.77
Retrieval	4.6 ± 6.7	2.6 ± 2.3	.00	1.00
Number of Trials to Criterion	3.1 ± 2.1	3.4 ± 1.9	−.63	.55

Total time: average drawing time per figure; error count: the number of errors; error time: time spent off the black line.

Table 2. Test Battery of Alertness and Vigilance (means ± SD)

	Controls (n = 13)	Patients (n = 16)	z	Mann–Whitney U Test p
Simple Alertness Task				
Reaction time (msec)	245.1 ± 43.9	248.5 ± 35.6	−.31	.78
Number of correct responses	77.2 ± 1.0	73.9 ± 10.8	−.28	.81
"Go/No Go" Task				
Reaction time (msec)	524.7 ± 74.5	554.5 ± 60.2	−1.65	.10
Number of correct responses	23.6 ± .5	23.4 ± 1.0	−.41	.75
Simple Reaction Task				
Reaction time (msec)	826.0 ± 150.8	826.2 ± 202.8	−.26	.81
Number of correct responses	93.9 ± 3.5	95.3 ± 2.4	−1.00	.33
Complex Reaction Task				
Reaction time (msec)	762.3 ± 128.7	766.7 ± 184.4	−.22	.85
Number of correct responses	29.5 ± 1.7	29.9 ± 1.0	−.39	.71
Vigilance Task				
Reaction time (msec)	605.7 ± 72.6	629.0 ± 118.4	−.09	.95
Number of correct answers	32.9 ± 2.8	33.3 ± 1.5	−.07	.95

the international 10-20 system. Electromyographic activity was recorded by submental electrodes. Vertical and horizontal eye movements were recorded by two horizontal electrodes and one vertical electrode. Furthermore, electromyographic recordings of the legs and three recordings of breathing (chest and abdominal excursions, nose-mouth airflow) together with oxygen monitoring were performed on the first night to rule out sleep apnea or periodic leg movements. No subject who had clinically relevant sleep apneas (> 5/hour) or nocturnal periodic leg movements with EEG-arousal (> 5/h) was enrolled in the study. Only data from the second (experimental) night were analyzed to compare the sleep EEG parameters of patients with those of control subjects. Sleep stages were scored according to standardized criteria (Rechtschaffen and Kales 1968) by experienced staff blind to the experimental condition. Sleep EEG analyses included the following parameters: sleep onset latency is defined as the time in minutes from lights-off to the first epoch of stage 2 sleep; sleep period time is the time in minutes from sleep onset latency to the last awakening during bedtime; total sleep time is the time in minutes of all epochs of sleep. The different sleep stages (stage 1, stage 2, stage 3, stage 4, SWS as the sum of stages 3 and 4, and rapid eye movement [REM] sleep) and the nightly wake time were calculated in minutes and in percent of bedtime. Sleep efficiency means the percentage of sleep during bedtime; REM latency is defined as the time in minutes from sleep onset to the first REM sleep period. Furthermore, the power density in the .75–4 Hz range was calculated.

To estimate sleep quality, the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al 1989) was used, with proven good test-retest reliability and validity in patients with primary insomnia and in healthy control subjects (Backhaus et al 2002a). Values ≥ 5 indicate a clinically relevant decrease in sleep quality.

Cortisol

Blood samples were centrifuged immediately after collection, and serum was stored at −80°C until analysis by radioimmunoassay (Diagnostic Products, Herrman Biermann, Bad Nauheim, Germany; sensitivity: .2 μg/dL; intra-assay coefficient of variation: ≤ 5%; inter-assay coefficient of variation: < 6.5%).

Data Reduction and Statistical Analyses

Overnight consolidation of the word-pair associates and the overnight gain in mirror-tracing were calculated such that positive values represented an increase in declarative memory (enhanced number of recalled word pairs) and procedural memory (enhanced speed, reduced error time, and reduced error count), respectively. Thus, overnight declarative memory consolidation was defined as morning retrieval values minus evening recall

Table 3. Sleep EEG Parameters and Sleep Questionnaire

	Controls (n = 13)	Patients (n = 16)	t [df = 27]	p
Bedtime (min)	473.1 ± 12.4	472.3 ± 7.8	.23	.82
Sleep Period Time (min)	457.4 ± 12.1	445.2 ± 26.7	1.53	.14
Total Sleep Time (min)	439.8 ± 17.5	390.3 ± 43.4	3.85	≤.001
Sleep Efficiency (%)	92.94 ± 2.50	82.63 ± 8.86	4.05	≤.001
Sleep Onset Latency (min)	14.96 ± 10.14	20.34 ± 23.60	−.77	.45
REM Latency (min)	109.04 ± 38.77	93.22 ± 44.66	1.01	.32
Wake Time %	6.01 ± 2.61	16.73 ± 8.85	−4.21	≤.001
Stage 1%	6.12 ± 4.27	6.71 ± 2.17	−.49	.63
Stage 2%	50.79 ± 12.23	48.94 ± 8.88	.47	.64
SWS (Stages 3 + 4)%	18.7 ± 14.1	9.9 ± 7.6	2.13	.04
Stage REM %	18.33 ± 5.58	17.58 ± 5.06	.38	.71
Pittsburgh Sleep Quality Index	2.2 ± 1.7	11.9 ± 3.5	−9.13	≤.001

Means ± SD, sleep stages in percent of bedtime.
EEG, electroencephalogram; REM, rapid eye movement (sleep); SWS, slow wave sleep.

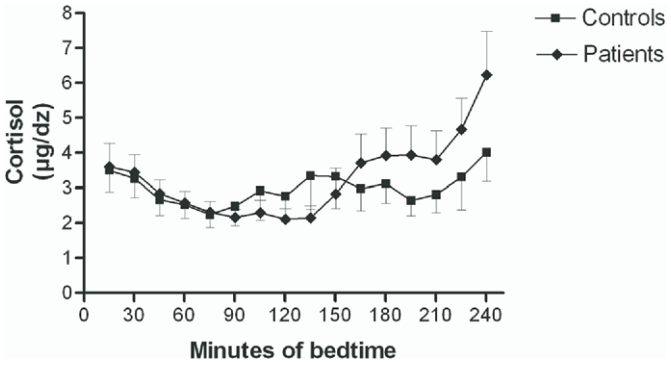

Figure 2. Serum cortisol concentrations during the night in patients and control subjects (means ± SEM).

values, whereas overnight procedural memory gain was defined as evening recall values minus morning retrieval values.

Group differences were analyzed by analyses of variance (ANOVAs), including a group factor (insomnia patients vs. control subjects) and, depending on the parameter, a time factor representing the different times of assessment (two time points for the declarative memory task, and 16 each for cortisol during the first- and the second half of the night). Technical problems caused missing data for mirror-tracing in four patients. The ANOVA across both groups on the cortisol values were calculated separately for the first- and the second half of the night, because: 1) the hypothesis referred exclusively to the association between hippocampus-dependent declarative memory consolidation and cortisol concentrations during the first half of the night, and 2) data on serum cortisol values for the second half of the night were missing for six patients and three control subjects. Post hoc *t*-tests were used to specify main and interaction effects of the ANOVA. The mirror-tracing task, the alertness test battery, and the power density in the .75–4 Hz range were calculated with nonparametric tests (Mann–Whitney *U* test and Wilcoxon test), because the variables showed no normal distribution. Sociodemographic and questionnaire data as well as data not repeatedly measured were analyzed with two-tailed *t*-tests for independent samples and chi-square tests, if appropriate. Owing to the age-dependence of memory processes, sleep EEG, and cortisol release, partial correlations between the variables were calculated controlling for age. An explorative regression analysis was calculated to explore the influence of different independent variables on declarative memory consolidation. The variables that correlated significantly with the consolidation of word pairs in the correlation analyses as well as the variable "age" were used as independent variables in the regression analysis. A p-value $< .05$ was set for significance. Data were analyzed with SPSS for Windows, Version 11. Variability values are expressed as SD unless otherwise specified.

Results

Subjects

There were no statistical differences between patients and control subjects in age (patients: 41.6 ± 1.2 years; control subjects: 40.1 ± 11.3 years; [$t(27) = -.36$, $p = .73$]), body mass index (patients: 23.1 ± 2.4; control subjects: 23.6 ± 3.5, [$t(27) = .49$, $p = .63$]), and years of education (patients: 14.4 ± 2.7; control subjects: 14.9 ± 3.6; [$t(27) = .59$, $p = .69$]). Mean duration of insomnia among patients was 9.2 ± 8.1 years.

Memory Tasks

Groups did not perform differently on the word-pair associates task in the learning phase in the evening before sleep, either with regard to the number of learning trials needed to reach the 60% criterion (patients: 1.9 ± .4; control subjects: 1.6 ± .6; [$t(27) = -1.58$, $p = .13$]), or with regard to the number of words correctly recalled in the last criterion trial [$t(27) = .23$, $p = .82$]. By contrast, their retrieval performance after the retention period after sleep differed significantly, with control subjects showing an overnight increase in recall and the patients showing an overnight recall decrease [$t(27) = 2.25$, $p = .03$]. The ANOVA for the paired associates task revealed a significant group × time interaction effect [$F(1,27) = 9.54$, $p = .005$] (Figure 1).

On the mirror-tracing task, patients and control subjects differed neither with regard to learning before sleep nor in their retrieval after sleep (Table 1). Performance improved in both groups after sleep (i.e., they needed less time to draw the figures; Wilcoxon test: control subjects, $z = -3.2$, $p = < .01$; patients, $z = -3.1$, $p = < .01$) and made fewer errors (error time: control subjects, $z = -3.1$, $p = < .01$; patients, $z = -2.9$, $p = < .01$; error count: control subjects, $z = -3.1$, $p = < .01$; patients, $z = -2.9$, $p = < .01$). However, none of these parameters was differentially affected in either group (see Table 1 for exact values and statistics).

Patients and control subjects did not differ in their performance of any task in the extensive standardized test battery of alertness and vigilance (TAP, Table 2), indicating that there were no differences in their respective alertness and vigilance.

Sleep EEG and Sleep Questionnaire

Patients had a significantly lower amount of SWS, significantly more wake time after sleep onset, and a decreased total sleep time as well as decreased sleep efficiency (Table 3). Groups did not differ with regard to the time spent in REM sleep and in stage 2 sleep. Patients and control subjects did not differ in their power density in the .75–4 Hz range (patients: 127.8 ± 61.7 μV^2/Hz; control subjects: 163.1 ± 130.0 μV^2/Hz; Mann–Whitney *U* Test: $z = -12$, $p = .93$). On the Pittsburgh Sleep Quality Index, patients estimated a significantly lower quality of sleep than did control subjects (Table 3).

Cortisol

Cortisol concentrations in both groups did not differ for either the first half of the night or for the second ([$F(1) = .27$, $p = .60$] for the group effect, and [$F(15,13) = .46$, $p = .922$] for time × group interaction effect of the first half of the night; [$F(1) = .49$, $p = .49$] for the group effect, and [$F(15,4) = .83$, $p = .64$] for the second half of the night; see Figure 2 for exact values).

Correlation Analyses

Partial correlation analyses (controlling for age) performed separately for control subjects and patients revealed a significant positive correlation between SWS and declarative memory consolidation (word-pair associates) among control subjects but not among insomnia patients (Figure 3). In contrast to the control subjects, declarative memory consolidation in the patients correlated significantly with the amount of REM sleep (Figure 3). There was no significant correlation in either group between total sleep time and declarative memory consolidation ($p > .05$). Correlation analyses of cortisol concentrations for the 1st, 2nd, 3rd, and 4th hours of the first half of the night revealed that higher values for declarative memory consolidation were significantly correlated in both groups with low serum cortisol levels at the end of the first half of the night, (i.e., during the last hour of the first half of the night; Figure 3).

The explorative regression analysis with the overnight consolidation of word pairs as dependent variable and age, SWS, REM sleep, and cortisol at the 4th hour of the night as indepen-

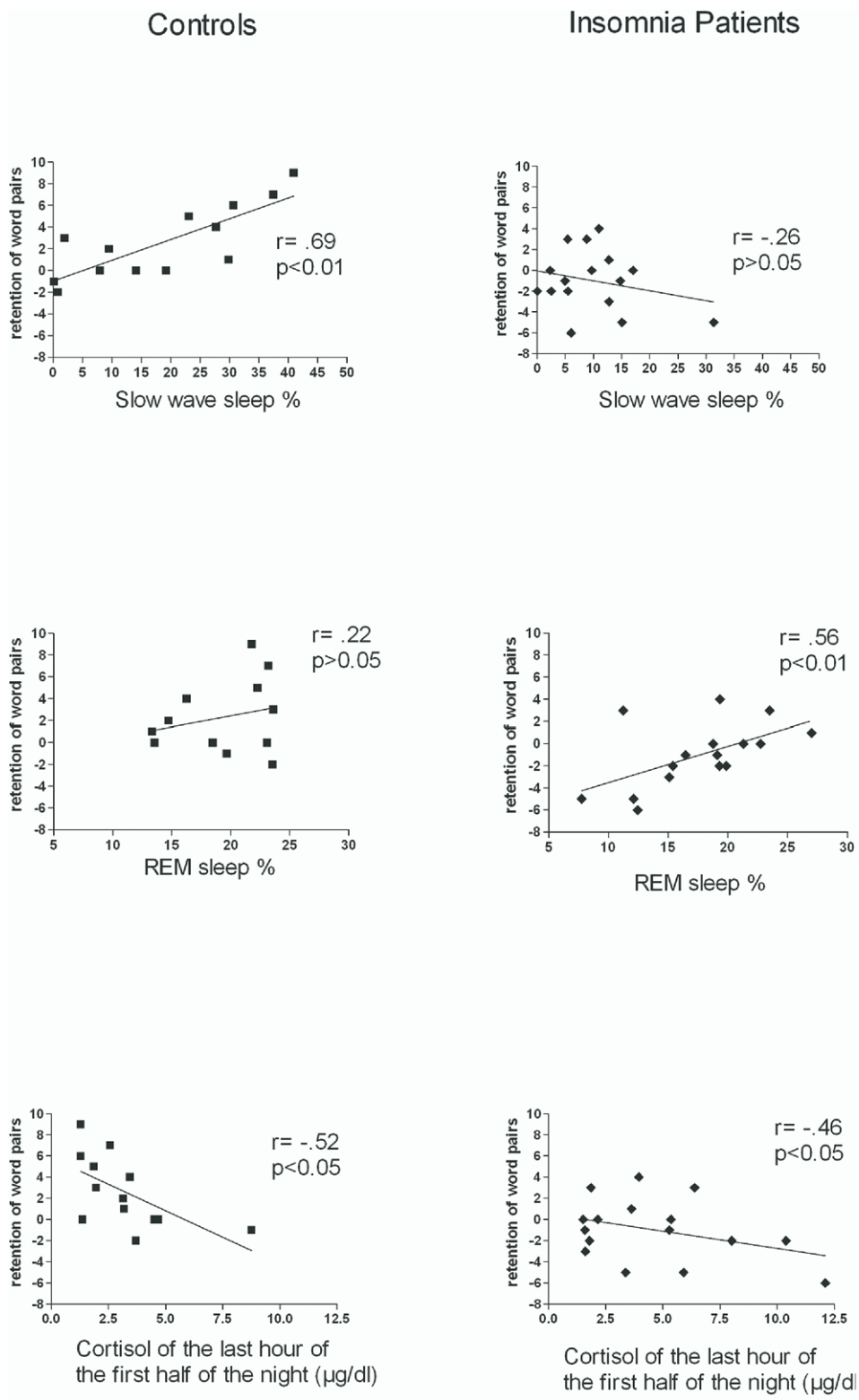

Figure 3. Partial correlation analyses (controlling for age) between consolidation of word pairs (indicated by the difference in recall at learning and retrieval testing) and SWS and REM sleep (in percentages of bedtime) and serum cortisol concentrations during the last hour of the first half of the night.

dent variables showed significant β coefficients for SWS, REM, and age (β: −.43, $p = .003$ for age; β: .39, $p = .025$ for SWS; β: .32, $p = .024$ for REM sleep) and a nearly significant β coefficient for cortisol (β: −.28, $p = .056$) on the overnight consolidation of the word-pair associates task.

Discussion

This study investigated the overnight sleep-dependent consolidation of both declarative and non-declarative memory in patients with primary insomnia. The results indicate a deficit of hippocampus-dependent declarative memory consolidation in these patients as opposed to healthy sleepers. Whereas in the healthy subjects declarative memory consolidation was positively correlated with SWS, the insomnia patients with a significantly lower amount of SWS showed no such association. By contrast, there was a significant correlation between declarative memory consolidation and REM sleep among the patients. Previous studies provide evidence that SWS contributes to the consolidation of declarative memory (Gais and Born 2004a, 2004b; Molle et al 2004; Peigneux et al 2004; Plihal and Born 1997, 1999; Yaroush et al 1971). However, the significant correlation of declarative memory consolidation with the amount of REM sleep in the insomnia patients suggests that REM sleep also might benefit the consolidation of declarative memory, although to a lesser degree than SWS in the control subjects. Another study also found an association between REM sleep and consolidation of declarative memory (Rauchs et al 2004). Because the correlation between REM sleep and declarative memory consolidation was observed in the present study only in the insomnia patients, REM sleep might play a partly compensatory role in declarative memory consolidation in conditions where the proportion of SWS is low. This would be of considerable relevance also for healthy elderly subjects, who, compared with young healthy subjects, display a strong decrease in SWS (Van Cauter et al 2000). However, because the majority of studies on sleep and memory have been conducted in young healthy subjects with naturally high amounts of SWS, this issue cannot yet be resolved. A replication of our findings in a larger sample and across different age groups would further substantiate our suggestion of a partly compensatory role in declarative memory consolidation of REM sleep where the amount of SWS is low.

Previous studies found either only slightly disturbed memory performance in insomnia patients when testing encoding and retrieval on the same day or none at all (e.g., Sateia et al 2000). The present data are in line with those results, because patients and control subjects had the same performance level in the memory tasks before sleep. This finding is important, because it rules out that among insomnia patients impaired declarative memory recall after retention sleep originated from a poor encoding of the word-pair associates. On the basis of these data, it is justifiable to conclude that the impaired retrieval of the word-pair associates by our patients reflects primarily a relevant impairment of the consolidation of declarative memory during retention sleep.

In both healthy subjects and insomnia patients, enhanced cortisol release during the last hour of the first half of the night was associated with disturbed consolidation of declarative memory. In light of evidence that the glucocorticoid feedback to hippocampal networks blocks sleep-associated consolidation of declarative memory (Plihal et al 1999), it has to be considered that suppression of cortisol release during the early night might contribute to the consolidation of memory during sleep. The association between enhanced cortisol levels and diminished overnight consolidation of declarative memory was found, despite the rather low overall variability in serum cortisol concentrations during early sleep, when these concentrations reach an absolute minimum. This indicates that even slight increases in pituitary-adrenal activity during this sleep period are paralleled by substantial decreases in declarative memory consolidation. However, in insomnia patients, serum cortisol concentrations during sleep did not differ significantly from those of control subjects for either the first or for the second half of the night. This result fits those of a previous study (Riemann et al 2002) but contrasts with others (Rodenbeck et al 2002; Vgontzas et al 2001). In the present study, the lack of a significant increase in sleep-associated cortisol release in the insomnia patients as opposed to control subjects indicates that cortisol release does not play a primary role in mediating the differences between the two groups in the overnight consolidation of declarative memory. In light of the missing group differences with regard to the nocturnal cortisol release, the differences in sleep architecture (especially the decreased SWS) seems to be of particular importance in explaining the different consolidation of declarative memory by patients and control subjects.

The sample size our study was larger than in other studies that investigated nocturnal cortisol release in insomnia patients (Riemann et al 2002; Rodenbeck et al 2002; Vgontzas et al 2001). Nonetheless, it has to be considered that this sample size still is associated with some risk of false negative results as to error count for retrieval in the mirror-tracing task, the number of correct responses for simple reaction time and simple alertness in the extensive alertness test battery, and the number of trials required to reach the criterion in the declarative memory task. However, with regard to declarative memory it must be emphasized that patients and control subjects showed practically identical performances on the last trial before sleep. Further studies using other tasks are needed to investigate whether the deficit is in fact selective for declarative memory or whether there are also differences in procedural memory consolidation or in alertness. Another interesting and important extension of this study would be to use a more extensive EEG recording overnight, allowing the detection of local changes in connection with memory consolidation. Thus Huber et al (2004) showed that procedural motor learning is related to local increase in slow wave activity, and Gais et al (2002) found an association of declarative learning with sleep spindles, especially at the vertex (Cz) electrode position during the subsequent night.

In conclusion, the central and novel result of this study is that memory consolidation in insomnia patients is impaired for hippocampus-dependent declarative memory materials. These patients often complain about memory problems, which they attribute to their disturbed sleep at night. Focusing on the role of sleep in the consolidation of memory, this study demonstrates that primary insomnia is indeed accompanied by distinct cognitive dysfunction that substantially disables these patients in their everyday life. In light of the high prevalence of primary insomnia of almost 20% (Backhaus et al 2002b; Leger et al 2000), our results are of considerable clinical relevance. Of the effective pharmacological (Nowell et al 1997) and non-pharmacological treatments (e.g., Irwin et al 2006; Morin et al 1994) for insomnia, particularly the non-pharmacological treatments have positive long-term effects on sleep quality, persisting over years (Backhaus et al 2001). Therefore it seems worthwhile to investigate whether sleep-related declarative memory consolidation improves after a successful insomnia therapy.

This study was supported by a grant from the Deutsche Forschungsgemeinschaft (to JBa and KJ; BA 2022/2).

We thank Jolanta Chwalko, Andrea Schlagelambers, and Michael Andrew for study assistance.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th ed. Washington, DC: American Psychiatric Press.

Backhaus J, Hohagen F, Voderholzer U, Riemann D (2001): Long-term effectiveness of a short-term cognitive-behavioral group treatment for primary insomnia. *Eur Arch Psychiatry Clin Neurosci* 251:35–41.

Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F (2002a): Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res* 53:737–740.

Backhaus J, Junghanns K, Hohagen F (2004): Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology* 29:1184–1191.

Backhaus J, Junghanns K, Mueller-Popkes K, Broocks A, Riemann D, Hajak G, Hohagen F (2002b): Short-term training increases diagnostic and treatment rate for insomnia in general practice. *Eur Arch Psychiatry Clin Neurosci* 252:99–104.

Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992): Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry* 49:651–668.

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989): The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 28:193–213.

de Quervain DJ, Roozendaal B, Nitsch RM, McGaugh JL, Hock C (2000): Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nat Neurosci* 3:313–314.

Ficca G, Salzarulo P (2004): What in sleep is for memory. *Sleep Med* 5:225–230.

Fischer S, Hallschmid M, Elsner AL, Born J (2002): Sleep forms memory for finger skills. *Proc Natl Acad Sci U S A* 99:11987–11991. Epub 2002 Aug 22.

Gais S, Born J (2004a): Declarative memory consolidation: mechanisms acting during human sleep. *Learn Mem* 11:679–685.

Gais S, Born J (2004b): Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proc Natl Acad Sci USA* 101:2140–2144.

Gais S, Molle M, Helms K, Born J (2002): Learning-dependent increases in sleep spindle density. *J Neurosci* 22:6830–6834.

Het S, Ramlow G, Wolf OT (2005): A meta-analytic review of the effects of acute cortisol administration on human memory. *Psychoneuroendocrinology* 30:771–784.

Huber R, Ghilardi MF, Massimini M, Tononi G (2004): Local sleep and learning. *Nature* 430:78–81

Hudson JI, Pope HG, Sullivan LE, Waternaux CM, Keck PE, Broughton RJ (1992): Good sleep, bad sleep: A meta-analysis of polysomnographic measures in insomnia, depression, and narcolepsy. *Biol Psychiatry* 32:958–975.

Irwin MR, Cole JC, Nicassio PM (2006): Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol* 25:3–14.

Kirschbaum C, Wolf OT, May M, Wippich W, Hellhammer DH (1996): Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci* 58:1475–1483.

Kuriyama K, Stickgold R, Walker MP (2004): Sleep-dependent learning and motor-skill complexity. *Learn Mem* 11:705–713.

Leger D, Guilleminault C, Dreyfus JP, Delahaye C, Paillard M (2000): Prevalence of insomnia in a survey of 12,778 adults in France. *J Sleep Res* 9:35–42.

Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP, et al (1997): Stress-induced declarative memory impairment in healthy elderly subjects: Relationship to cortisol reactivity. *J Clin Endocrinol Metab* 82:2070–2075.

Maquet P (2001): The role of sleep in learning and memory. *Science* 294:1048–1052.

Molle M, Marshall L, Gais S, Born J (2004): Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. *Proc Natl Acad Sci USA* 101:13963–13968.

Morin C, Rodrigue S, Ivers H (2003): Role of stress, arousal, and coping skills in primary insomnia. *Psychosom Med* 65:259–267.

Morin CM, Culbert JP, Schwartz SM (1994): Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry* 151:1172–1180.

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL (1999): Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry* 56:527–533.

Nowell PD, Buysse DJ, Reynolds CF, Hauri PJ, Roth T, Stepanski EJ, et al (1997): Clinical factors contributing to the differential diagnosis of primary insomnia and insomnia related to mental disorders. *Am J Psychiatry* 154:1412–1416.

Peigneux P, Laureys S, Delbeuck X, Maquet P (2001): Sleeping brain, learning brain. The role of sleep for memory systems. *Neuroreport* 12:A111–A124.

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, et al (2004): Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron* 44:535–45.

Plihal W, Born J (1997): Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci* 9:534–547.

Plihal W, Born J (1999a): Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology* 36:571–582.

Plihal W, Born J (1999b): Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *Neuroreport* 10:2741–2747.

Plihal W, Pietrowsky R, Born J (1999): Dexamethasone blocks sleep induced improvement of declarative memory. *Psychoneuroendocrinology* 24:313–331.

Rauchs G, Bertran F, Guillery-Girard B, Desgranges B, Kerrouche N, Denise P, et al (2004): Consolidation of strictly episodic memories mainly requires rapid eye movement sleep. *Sleep* 27:395–401.

Rauchs G, Desgranges B, Foret J, Eustache F (2005): The relationships between memory systems and sleep stages. *J Sleep Res* 14:123–140.

Rechtschaffen A, Kales A (1968): *A Manual of Standardised Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles, California: Brain Research Institute, UCLA.

Riemann D, Klein T, Rodenbeck A, Feige B, Horny A, Hummel R, et al (2002): Nocturnal cortisol and melatonin secretion in primary insomnia. *Psychiatry Res* 113:17–27.

Rodenbeck A, Huether G, Ruther E, Hajak G (2002): Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neurosci Lett* 324:159–163.

Sateia MJ, Doghramji K, Hauri PJ, Morin CM (2000): Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep* 23:243–308.

Smith C (2001): Sleep states and memory processes in humans: Procedural versus declarative memory systems. *Sleep Med Rev* 5:491–506.

Smith C, MacNeill C (1994): Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. *J Sleep Res* 3:206–213.

Stickgold R, Hobson JA, Fosse R, Fosse M (2001): Sleep, learning, and dreams: off-line memory reprocessing. *Science* 294:1052–1057.

Van Cauter E, Leproult R, Plat L (2000): Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *JAMA* 284:861–868.

Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, et al (2001): Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab* 86:3787–3794.

Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002): Practice with sleep makes perfect: Sleep-dependent motor skill learning. *Neuron* 35:205–211.

Walker MP, Brakefield T, Seidman J, Morgan A, Hobson JA, Stickgold R (2003): Sleep and the time course of motor skill learning. *Learn Mem* 10:275–284.

Walker MP, Stickgold R (2004): Sleep-dependent learning and memory consolidation. *Neuron* 44:121–133.

Walker MP, Stickgold R, Alsop D, Gaab N, Schlaug G (2005): Sleep-dependent motor memory plasticity in the human brain. *Neuroscience* 133:911–917.

Yaroush R, Sullivan MJ, Ekstrand BR (1971): Effect of sleep on memory. II. Differential effect of the first and second half of the night. *J Exp Psychol* 88:361–366.

Zimmermann P, Fimm B (1993): *Testbatterie zur Aufmerksamkeitstestung (TAP)*. Würselen, Germany: Psytest.