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Declarative memory consolidation during the first night in a sleep lab: The role of REM sleep and cortisol

Monique Goerke [a,b,c,1,*], Stefan Cohrs [a,d,1], Andrea Rodenbeck [a,d], Ulrike Grittner [e], Werner Sommer [c], Dieter Kunz [a,f]

[a] *Sleep Research & Clinical Chronobiology, Department of Physiology (CBF), Charité — Universitätsmedizin Berlin, 14195 Berlin, Germany*
[b] *German Center for Neurodegenerative Diseases, 39120 Magdeburg, Germany*
[c] *Department of Psychology, Humboldt University, 12489 Berlin, Germany*
[d] *Department of Psychiatry and Psychotherapy, Georg August University, 37075 Göttingen, Germany*
[e] *Department of Biometrics and Clinical Epidemiology, Charité — Universitätsmedizin Berlin, 10117 Berlin, Germany*
[f] *German Heart Institute Berlin, 13353 Berlin, Germany*

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Summary While the consolidation of declarative memory is supported by slow wave sleep (SWS) in healthy subjects, it has been shown to be associated with rapid eye movement (REM) sleep in patients with insomnia. Sleep during a subject's first night in an unfamiliar environment is often disturbed, and this so-called first-night effect (FNE) has often been used as a model of transient insomnia. Additionally, sleeping for the first time in an unfamiliar environment can lead to increased cortisol secretion, and declarative memory consolidation likely depends on low cortisol levels, especially during the early part of the night. Accounting for intersubject variability in the FNE, we examined the relationship between sleep stages, cortisol secretion and declarative memory performance in 27 healthy young men. Declarative memory performance improved significantly after sleep. Whereas memory performance during the learning session and retrieval testing was strongly associated with cortisol secretion, the overnight gain was not. Post hoc analyses indicated that the overnight gain appears to be modulated by the extent of the FNE: a significant overnight improvement in memory performance was found only in subjects with a weak FNE ($n = 12$). In these subjects, no association was found between any sleep stage and the improvement observed in their memory performance. In subjects with a strong FNE ($n = 12$), however, the overnight change in memory performance was associated with the proportion of REM sleep and the total number of REMs. Disturbed sleep in an unfamiliar environment therefore appears to affect the memory consolidation process.

* Corresponding author at: German Center for Neurodegenerative Diseases (DZNE), Leipziger Str. 44, Haus 15, 39120 Magdeburg, Germany. Tel.: +49 391 67 24529; fax: +49 391 67 24528.
E-mail address: monique.goerke@dzne.de (M. Goerke).
[1] These authors contributed equally to this work.

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1. Introduction

There is growing evidence that sleep plays a crucial role in memory consolidation (Diekelmann and Born, 2010). For declarative memory, which involves the conscious recall of facts and events, non-REM sleep (sleep stages 2–4) and especially slow wave sleep (SWS, sleep stages 3 and 4) appear to be of great importance. Taking advantage of the uneven distribution of sleep stages throughout the night, several studies have shown that subjects performed better on a word pair association task after sleeping the first half of the night, which is rich in SWS, than they did after sleeping the second half of the night, in which REM sleep predominates (Yaroush et al., 1971; Barrett and Ekstrand, 1972; Fowler et al., 1973; Plihal and Born, 1999a). Given that the proportion of time spent in stage 2 sleep is comparable in both halves of the night, it was possible in these studies to rule out a primary role for stage 2 sleep (Fowler et al., 1973; Plihal and Born, 1999a). Along these lines, performance on a word pair association task improved in subjects who slept only the first half of the night to the same extent as it did in subjects who had a full night of sleep, indicating that the first hours of sleep confer the greatest memory improvement (Tucker and Fishbein, 2009). Moreover, transcranial direct current stimulation, which enhances the slow oscillations that characterize SWS, has been found to improve recall in a word pair association task (Marshall et al., 2004, 2006). In contrast, a significant correlation between declarative memory performance and the proportion of REM sleep in insomnia patients was demonstrated by Backhaus et al. (2006), who suggest that this may be due to a compensatory mechanism in disturbed sleep.

The results of half-night experiments, however, may be influenced by factors other than sleep, such as those subject to circadian organization. Importantly, declarative memory consolidation is also modulated by the secretion of cortisol (Het et al., 2005; Wolf, 2009). The activity of the hypothalamic-pituitary-adrenocortical (HPA) axis displays a circadian rhythm, which is reflected in high levels of cortisol secretion in the early morning, a decline throughout the day, a prolonged quiescent period of low levels centered around midnight, and a rapid rise during the second half of the night (Weitzman et al., 1971; Van Cauter and Refetoff, 1985). The circadian rhythm of cortisol secretion is also influenced by sleep. Sleep onset appears to have an inhibitory effect on cortisol secretion that persists for one to two hours (Van Cauter and Refetoff, 1985; Born et al., 1988), and low cortisol levels have been shown to be associated with a greater proportion of SWS (Follenius et al., 1992). It is still a matter of debate, however, whether SWS inhibits the activity of the HPA axis or whether decreased HPA tone promotes deep sleep (Balbo et al., 2010). Nocturnal awakenings are related to pulsatile releases of cortisol, followed by a temporary inhibition of cortisol secretion (Späth-Schwalbe et al., 1991; Follenius et al., 1992), whereas the final morning awakening elicits a marked and rapid rise in cortisol levels persisting for about 60 min independent of whether the awakening occurs spontaneously or is triggered externally (Pruessner et al., 1997).

In recent studies, the interaction between cortisol secretion and sleep has also been investigated in relation to memory consolidation. Enhancing glucocorticoid activity during the first half of the night by intravenously administering hydrocortisone has been shown to impair the consolidation of declarative memory for word pairs (Plihal and Born, 1999b). Correspondingly, administering the glucocorticoid receptor agonist dexamethasone blocked the beneficial effect of early, SWS-rich sleep on the recall of word pairs (Plihal et al., 1999). Moreover, in patients suffering from primary insomnia, several studies have found that cortisol levels are elevated, especially in the early part of the night (Vgontzas et al., 2001; Rodenbeck et al., 2002) and that word pair recall after sleep was poor (Backhaus et al., 2006).

A subject's first night in a sleep laboratory differs from subsequent nights in terms of sleep architecture: total sleep time (TST), time spent in REM sleep, and sleep efficiency are diminished, whereas REM latency and intermittent wake time are increased (Agnew et al., 1966; Browman and Cartwright, 1980; Toussaint et al., 1995). This well-known first-night effect, which appears to vary in magnitude between individuals, has often been used as a model of transient insomnia (Roehrs et al., 1990; Roth et al., 1995; Erman et al., 2004; Rosenberg et al., 2007; Zammit et al., 2009). In addition to sleep, other biological systems, such as the HPA axis, may also be altered by the first-night effect. The HPA axis is one of the most important mediators of an organism's response to acute physical and psychological stress, which leads to increased cortisol secretion. In addition to varying degrees of sleep disturbance, sleeping for the first time in a sleep laboratory may lead to increased cortisol secretion in some subjects, resulting in substantial variability both in sleep parameters and cortisol levels. The aim of the present study was to examine the interaction between sleep stages, cortisol secretion and sleep-dependent memory consolidation during the first night in a sleep lab. We hypothesized that declarative memory performance would be associated with the proportion of time spent in REM sleep rather than with the proportion of time spent in SWS. We also expected that high cortisol levels would be associated with worse performance on the memory task.

2. Methods

2.1. Subjects

A total of 32 healthy male subjects aged 18–39 years (mean: 27.3 years) were included in the study. The study protocol was approved by the local ethics committee. All subjects provided written informed consent and underwent physical and mental health examinations before participating. None had a history of drug or alcohol abuse, or of neurological, psychiatric, or sleep disorders. As confirmed by the Pittsburgh Sleep Quality Index (Buysse et al., 1989), no subject had suffered from poor sleep within four weeks prior to study entry (mean Pittsburgh Sleep Quality Index: 2.9). As confirmed by the Munich Chronotype Questionnaire (Roenneberg et al., 2003), none of the subjects demonstrated an extreme chronotype (mean Munich Chronotype Questionnaire score: 3.9). All subjects were accustomed to going to bed between 2200 h and 2400 h and to rising between 0600 h and 0800 h. Of the 32 subjects, 28 were non-smokers and four were smokers. Subjects were instructed to abstain (a) from taking any medication during, and at least eight days prior to, study

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participation and (b) from consuming caffeine or so-called energy drinks after 1200 h on the day they checked into the sleep laboratory for polysomnographic recording.

2.2. Experimental design and procedure

The present investigation was part of a larger study. During the first eight days, subjects slept at home, maintaining regular sleep schedules as confirmed by sleep logs and actigraphy (Actiwatch, Cambridge Neurotechnology). At 2000 h on the ninth day, they performed a word pair association task. Subsequently, subjects were prepared for polysomnographic recording, which started at 2300 h and ended, on the tenth day, at 0700 h. Urine produced between 2000 h on the ninth day and 0700 h on the tenth day was collected to measure cortisol excretion (see below). Retrieval on the memory task was tested between 0700 h and 0730 h on the tenth day.

2.3. Sleep log data

Using a sleep log, subjects documented (a) the time they went to bed, (b) the time they turned off the lights for sleep, (c) their estimated sleep latency, (d) the estimated time they spent awake after sleep onset, and (e) the time they woke up. Total sleep time was calculated for each of the seven nights prior to the night in the sleep laboratory (time from lights off to the final awakening minus sleep latency minus the time spent awake after sleep onset). Sleep log data were visually validated using the actigraphy data.

2.4. Memory task

The word pair association task consisted of a list of 44 pairs of semantically related German words (Gais and Born, 2004). During the learning session, the word pairs were presented on a computer screen for 5 s each, separated by intervals of 100 ms. After the entire list was completed, the first word from one of the pairs was displayed, and the subject had to name the associated word (cued recall). Regardless of whether the response was correct, the associated word was subsequently presented for 2 s to allow for re-encoding of the correct word pair. This procedure was repeated until the subject reached a criterion of 60% correct responses (24 word pairs). To rule out primacy and recency effects, the first and the last two words from the list served as buffer items that were not included in the analysis. Retrieval was tested using the cued recall procedure without correction.

2.5. Urine collection and hormone analysis

Subjects were provided with a urine container. For conservation of the urine samples, 10 ml of approximately 3% (w/v) hydrochloric acid per 500 ml urine were added to the urine container. Before the collection period started, subjects emptied their bladder. Afterwards, all the urine produced from 2000 h to 0700 h (including morning urine) was collected in the container. The volume of the total amount of urine produced was measured, and an aliquot of 20 ml was frozen at $-32\ ^{\circ}C$.

Urinary cortisol was measured by radioimmunoassay after steroid extraction using dichloromethane. Cortisol secretion was calculated for each subject as the product of urine volume and hormone concentration. Since the length of the collection period varied by 65 min (643—708 min, mean 681 ± 16.8 min), cortisol secretion was expressed as cortisol secretion per hour (the ratio of the total amount of cortisol secreted and the length of the collection period).

2.6. Polysomnographic recording and sleep data analysis

Sleep was polygraphically recorded using Sagura Polysomnograph 2000 (Dr. Sagura RMS AG). The recordings were performed using standard filter settings and included six electroencephalogram (EEG) channels (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), two electrooculogram (EOG) channels, a chin (mental) electromyography (EMG) channel, an EMG channel for the tibialis anterior muscle of each leg, and one for electrocardiography (ECG). In addition, nasal air flow, thoracic and abdominal excursion, peripheral oxygen saturation, and rectal (core body) temperature were measured. Sleep was scored according to the standardized criteria of Rechtschaffen and Kales in 30-s epochs by two experienced scorers who were blind to the results of the memory tasks (Rechtschaffen and Kales, 1968). For the total time in bed (TIB; i.e. time from lights off to lights on), every epoch was scored as (a) wake, (b) non-REM sleep stage 1, 2, 3, or 4, or (c) REM sleep. Time spent in non-REM stages 3 and 4 was defined as SWS. To account for time spent awake, we defined the percentage of a sleep stage as the percentage of TIB. Moreover, sleep onset was defined as the first epoch of stage 2 sleep; end of sleep as the first epoch of wake without a subsequent epoch of sleep; sleep period time (SPT) as time from sleep onset to the end of sleep; total sleep time (TST) as SPT minus wake after sleep onset; and sleep efficiency as the ratio between TST and TIB. Rapid eye movements during REM sleep were scored visually (see Khalsa et al., 2002 for details), yielding the total number of REMs and the REM density (mean number of REMs per epoch REM). All REMs were scored by the same rater (M.G.).

2.7. Statistical analysis

Five subjects were excluded from the analysis: one because of an abnormal electroencephalogram (epileptic potentials), two because they were unable to reach the learning criterion within three attempts during the learning session, and two because the retrieval testing in the morning was not conducted at the scheduled time. Memory task data were available for 27 subjects. Due to an incomplete report of sleep-wake patterns prior to the study in one case, sleep log data were available for 26 subjects; due to technical difficulties with polysomnography in two cases, polysomnographic data were available for 25 subjects; and due to deficient urine collection in one case, cortisol data were available for 26 subjects. We therefore performed some analyses using different numbers of subjects (i.e., 24 datasets when we compared sleep log data and polysomnographic data; 27 datasets when we analyzed memory performance alone; 26 datasets when we analyzed cortisol secretion alone; and 24 datasets in

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a combined analysis of memory performance, polysomnographic parameters and cortisol secretion). Data were analyzed using PASW Statistics 18 (SPSS Inc.) and SAS 9.2 (SAS Institute Inc.).

Variables were tested for normal distribution using the Shapiro–Wilk test. Correlative analyses were performed using Pearson's correlation coefficient. Comparative analyses were performed using dependent *t* tests within groups and independent *t* tests between groups (denoted by a lowercase "*t*") if the data were normally distributed; otherwise exact Wilcoxon (within groups, denoted by an uppercase "*T*") or exact Mann–Whitney *U* tests (between groups) were conducted. We calculated linear mixed models (Verbeke and Molenberghs, 2000) for the outcome test score, where the two time points of measurement (i.e., learning session and retrieval testing) were level-one units nested in the different individuals, who were the level-two units. We used a random intercept model (M1) without additional covariates to calculate the intraclass correlation, which indicates how two measures for the same individual are related to one another. Model M2 included information about cortisol secretion per hour; time spent awake during TIB; stage 1 and stage 2 sleep; and SWS and REM sleep. Model M3 additionally considered the cross-level interaction between REM sleep and the two time points of measurement.

3. Results

3.1. First-night effect

Table 1 shows (a) baseline data from seven nights prior to the night in the sleep laboratory, as confirmed by sleep logs, (b) polysomnographic data from the night in the sleep laboratory, and (c) normative polysomnographic data from a sample of 18 males of comparable age (from Ehlers and Kupfer, 1997). A comparison of baseline data with normative polysomnographic data revealed that total sleep time and sleep latency appeared to be highly comparable, whereas the time spent awake after sleep onset was lower in our subjects' sleep log data. A comparison of baseline data with the polysomnographic data from the night in the sleep laboratory revealed a significant decrease in total sleep time ($T = 7$, $P < 0.001$) and a significant increase in sleep latency ($T = 78$, $P = 0.039$), suggesting a pronounced first-night effect. This interpretation is supported by the clearly lower proportion of time spent in REM sleep by our subjects during their first laboratory night compared to the normative data.

3.2. Memory performance

The number of words recalled in the criterion trials of the learning session was positively associated with the number of words recalled during retrieval testing ($r = 0.579$, $P = 0.002$). The results of our linear mixed model (M1) indicate that subjects recalled an average of 2.67 more words during retrieval testing than during the learning sessions, representing a significant improvement ($P < 0.001$, see Table 2).

3.3. Memory performance and cortisol

The number of words recalled in the criterion trials of the learning session and the number of words recalled during retrieval testing were negatively associated with cortisol secretion per hour ($r = -0.476$, $P = 0.014$ and $r = -0.533$, $P = 0.005$, respectively; see Fig. 1).

In contrast, the overnight change in memory performance, which is referred to henceforth as the performance delta and was calculated from raw scores or percentages, was not associated with cortisol secretion per hour (both *P* values >0.306). After extending the linear mixed model to include information about (a) cortisol secretion per hour, (b)

Table 1 Baseline sleep data (based on sleep logs), polysomnographic data and normative polysomnographic data. Means and standard deviations are shown. REM: rapid eye movement; SWS: slow wave sleep.

	Baseline data (mean of seven nights prior to the night in the sleep laboratory as confirmed by sleep logs), $n = 24$	Polysomnographic data (night in the sleep laboratory), $n = 24$	Normative polysomnographic data from Ehlers and Kupfer (1997) (no SD provided), $n = 18$
Sleep latency (min)	15.25 ± 8.11	29.14 ± 32.59	14.44
Wake after sleep onset (min)	4.58 ± 5.57	47.46 ± 37.48	15.5
Total sleep time (min)	451.98 ± 24.80	394.54 ± 61.95	447.83
S1 (min)	n/a	41.94 ± 23.07	n/a
S2 (min)	n/a	214.42 ± 53.04	n/a
SWS (min)	n/a	66.02 ± 30.68	65.95
REM sleep (min)	n/a	68.80 ± 21.02	125.06
Total REMs	n/a	369.95 ± 196.87	n/a
REM density	n/a	2.71 ± 1.41	1.47
S1% total sleep time (TST)	n/a	11.06 ± 6.19	4.62
S2% TST	n/a	53.90 ± 8.94	52.73
SWS % TST	n/a	16.53 ± 6.91	14.54
REM % TST	n/a	17.62 ± 4.88	28.11

n/a: not applicable.

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Table 2 Linear mixed models for the outcome test score, where the two points of measurement (i.e., during the learning session and retrieval testing) are level-one units nested in the different individuals, who are the level-two units.

	M1 Random intercept (27 individuals, 54 observations)	M2 +Cortisol, wake, S1 sleep, S2 sleep, SWS, REM sleep (24 individuals, 48 observations)	M3 +Cross-level interaction (24 individuals, 48 observations)
Fixed part	β, significance	β, significance	β, significance
Constant	28.04; $P < 0.0001$	28.09; $P < 0.0001$	28.12; $P < 0.0001$
Time point (recalled words during learning session and retrieval testing)	2.67; $P < 0.001$	2.54; $P = 0.001$	2.52; $P = 0.001$
Cortisol (centered; 1000th)		−2.60; $P = 0.014$	−3.02, $P = 0.001$
Wake (centered)		−0.06; $P = 0.958$	
S1 sleep (centered)		−0.19; $P = 0.857$	
S2 sleep (centered)		−0.11; $P = 0.918$	
SWS (centered)		0.01; $P = 0.996$	
REM sleep (centered)		0.08; $P = 0.936$	0.05; $P = 0.717$
REM sleep × time point			0.27; $P = 0.079$
Random part			
Variance of individuals	6.40; $P < 0.007$	3.78; $P = 0.055$	3.79; $P = 0.033$
Residual variance	5.08; $P < 0.001$	5.43; $P < 0.001$	4.92; $P < 0.001$
ICC	0.56	0.41	0.43
−2LL	271.4	237.6	231.7

Centered: we transformed the data so that they were centered around mean "0"; 1000th: every value was then divided by 1000 to avoid very small and difficult to interpret regression coefficients. SWS: slow wave sleep; REM sleep: rapid eye movement sleep.

the time spent awake during TIB, and (c) the proportion of time spent in stage 1 sleep, stage 2 sleep, SWS and REM sleep as predictors (M2), cortisol secretion per hour was found to be significant ($\beta = -2.60$, $P = 0.014$). Our analyses of possible interactions between HPA axis activity and sleep parameters revealed that there was no association between cortisol secretion per hour and the proportion of time spent in SWS or REM sleep (both P values > 0.131). To further understand the putative role played by cortisol, we divided the sample at the median into groups with low ($n = 13$) or high ($n = 13$) cortisol secretion per hour. Both groups recalled significantly more words during retrieval testing than during the learning session [low cortisol level: $M = 31.77 \pm 3.62$ versus 29.00 ± 2.65 words, $t(12) = -4.382$, $P < 0.001$; high cortisol level: $M = 29.69 \pm 4.01$ versus 27.00 ± 2.97 words, $t(12) = -2.385$, $P = 0.034$]. Neither group differed in terms of the proportion of time spent in SWS or any other sleep stage (all P values > 0.210).

3.4. Memory performance and sleep

The performance delta was not associated with total sleep time or sleep efficiency (all P values >0.550), nor was it associated with the proportion of time spent in SWS (both P values >0.191). There was, however, a trend towards an association between the performance delta and the proportion of time spent in REM sleep (raw score delta: $r = 0.372$, $P = 0.067$; delta in percent: $r = 0.362$, $P = 0.076$). When we included the cross-level interaction between REM sleep and the two time points of measurement (i.e., learning session and retrieval testing) in a third linear mixed model (M3), a trend towards an interaction between the proportion of time spent

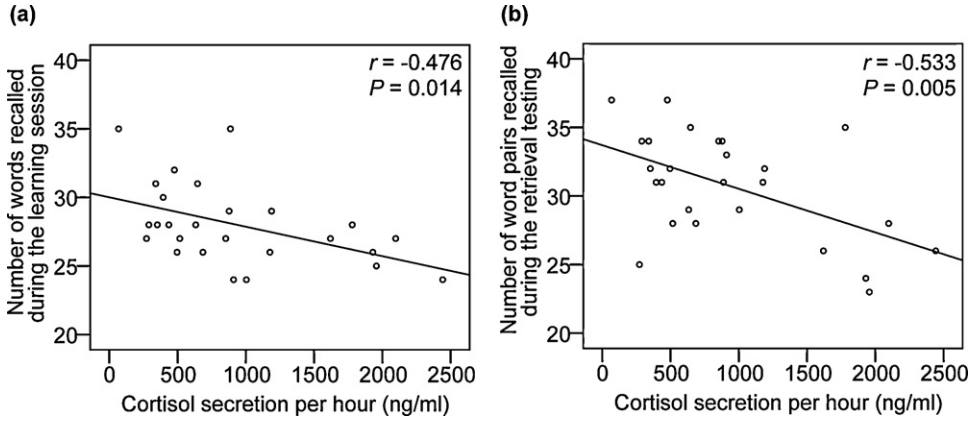

Figure 1 Correlations between (a) memory performance during the criterion trials of the learning session and cortisol secretion per hour and (b) memory performance during retrieval testing and cortisol secretion per hour.

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Table 3 Baseline sleep data, memory performance data and polysomnographic data from the first night in the sleep laboratory for the groups with a weak and a strong first-night effect (FNE) and *P* values for the comparative analyses.

	Weak first night effect, $n = 12$	Strong first night effect, $n = 12$	*P*-value
Baseline total sleep time (min)	445.21 ± 24.38	457.43 ± 26.59	0.253[a]
Baseline sleep latency (min)	15.29 ± 5.78	15.5 ± 10.31	0.951[a]
Pittsburgh Sleep Quality Index	3.00 ± 1.21	2.92 ± 1.51	0.882[a]
Number of words recalled in the criterion trials during learning session	28.67 ± 3.80	27.75 ± 1.76	0.785[b]
Number of words recalled during retrieval testing	31.42 ± 3.75	30.08 ± 4.19	0.503[b]
Number of trials needed to reach the 60% criterion during learning session	2.33 ± 0.65	2.17 ± 0.83	0.777[b]
Sleep latency (min)	20.46 ± 11.58	37.13 ± 45.00	0.193[b]
Wake (min)	25.71 ± 16.55	67.25 ± 42.40	0.001[b]
S1 (min)	33.00 ± 20.51	50.67 ± 23.88	0.050[b]
S2 (min)	246.96 ± 34.79	181.58 ± 50.94	0.001[b]
SWS (min)	66.92 ± 18.07	67.83 ± 40.32	0.724[b]
REM sleep (min)	74.17 ± 24.23	63.42 ± 17.72	0.284[b]
REM latency (min)	136.83 ± 49.54	167.79 ± 71.66	0.242[b]
Total REMs	424.75 ± 194.56	296.89 ± 185.31	0.169[b]
REM density	3.01 ± 1.53	2.31 ± 1.21	0.226[b]
Wake % time in bed (TIB)	10.03 ± 4.89	21.99 ± 16.33	0.001[b]
S1% TIB	7.54 ± 4.51	11.50 ± 5.42	0.052[b]
S2% TIB	52.02 ± 7.32	38.14 ± 10.71	0.001[b]
SWS % TIB	14.09 ± 3.80	14.27 ± 8.52	0.755[b]
REM sleep % TIB	15.62 ± 5.09	13.33 ± 3.78	0.291[b]
Cortisol secretion per hour	804.57 ± 640.92	1116.44 ± 732.70	0.525[b]

Means and standard deviations are shown. REM: rapid eye movement; SWS: slow wave sleep.
[a] Independent *t* test.
[b] Mann–Whitney *U* test.

in REM sleep and time point of measurement was observed ($\beta = 0.27$, $P = 0.079$).

3.5. Extent of first-night effect, memory performance, sleep, and cortisol

To explore these results further, we divided the sample into groups with a strong or a weak first-night effect. A strong first-night effect was defined as experiencing a decrease of more than 10% in total sleep time during the night in the sleep laboratory compared to the baseline measurements. A weak first-night effect was defined as experiencing a decrease in total sleep time of less than 10%. Importantly, neither of the groups ($n = 12$ in each) differed substantially in its baseline total sleep time or sleep latency, nor in its sleep quality four weeks prior to the study, as measured by the Pittsburgh Sleep Quality Index (see Table 3 for details).

Subjects in the group with a weak first-night effect significantly improved their memory performance from the learning session to retrieval testing ($T = 9.5$, $P = 0.019$). In contrast, within the group with a strong first-night effect, only a trend towards a significant improvement was observed ($T = 15$, $P = 0.061$). Differences in the overnight change in memory performance cannot be attributed to the number of learning trials needed to reach the 60% criterion during learning session (Table 3).

Polysomnographic data from the night in the sleep laboratory revealed a higher proportion of stage 2 sleep in the group with a weak first-night effect than in the group with a strong first-night effect ($U = 16$, $P = 0.001$). Neither group differed significantly in any other sleep stage proportions or in the number of REMs/REM density (Table 3). Within the group with a strong first-night effect, the overnight change in memory performance was associated with the proportion of time spent in REM sleep (raw score delta: $r = 0.672$, $P = 0.017$; delta in percent: $r = 0.670$, $P = 0.017$) or the total number of REMs (raw score delta: $r = 0.727$, $P = 0.026$; delta in percent: $r = 0.738$, $P = 0.023$). Within the group with a weak first-night effect, however, no association was observed between REM sleep or SWS and an improvement in memory performance. Cortisol secretion per hour did not differ substantially between the two groups ($P = 0.525$, see Table 3).

4. Discussion

Sleep during a subject's first night in an unfamiliar environment is often disturbed, and this first-night effect has often been used as a model of transient insomnia. In the present study, we found that the extent of the first-night effect was associated with sleep dependent memory consolidation as measured by a declarative word pair association task. A significant overnight improvement in memory performance

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was observed only in subjects with a weak first-night effect. Moreover, among these subjects, there was no association between any sleep stage and the improvement observed in memory performance. In contrast, among subjects with a strong first-night effect, the overnight change in memory performance was associated with the proportion of time spent in REM sleep and the total number of REMs. Additionally, memory performance during the learning session and retrieval testing was strongly associated with cortisol secretion, while the overnight gain was not.

Our finding that the overnight change in declarative memory performance was significantly associated with the proportion of REM sleep among subjects with a strong first-night effect is at variance with a range of studies that have demonstrated a relationship between declarative memory consolidation and SWS (Yaroush et al., 1971; Barrett and Ekstrand, 1972; Fowler et al., 1973; Plihal and Born, 1999a; Tucker et al., 2006; Lahl et al., 2008; Tucker and Fishbein, 2008, 2009). It is, however, in line with the results reported by Backhaus et al. (2006), who showed a significant association between declarative memory performance and the proportion of time spent in REM sleep in insomnia patients. The first-night effect has been used for nearly two decades as a model for transient insomnia (Roehrs et al., 1990; Roth et al., 1995; Erman et al., 2004; Rosenberg et al., 2007; Zammit et al., 2009). Our finding lends further support to this model, suggesting that sleep disturbances in insomnia patients and sleep disturbances provoked by sleeping in an unfamiliar environment affect the memory consolidation process in a similar way.

In addition to the important role played by REM sleep in declarative memory consolidation, Backhaus et al. (2006) found a significantly lower proportion of SWS in insomnia patients than in healthy controls, leading them to suggest that REM sleep may play a compensatory role in declarative memory consolidation in cases where the proportion of SWS is low. In the present study, however, we did not observe such an association between performance delta and SWS. Moreover, subjects with a weak first-night effect did not differ from those with a strong first-night effect with regard to the proportion or absolute amount of SWS.

Furthermore, REM sleep has been reported to be critical to the consolidation of memory if the processed information is emotionally salient (Wagner et al., 2001, 2007; Nishida et al., 2009). Along these lines, it has been proposed that during wake state, hippocampal-bound information is encoded within cortical modules. During REM sleep, these neural structures are reactivated, which is made possible by synchronous theta oscillations throughout these networks. This reactivation leads to a strengthening of cortico-cortical connections and/or promotes their integration into pre-existing experiences, allowing the experiences to become independent of the hippocampus (Walker and van der Helm, 2009). Fogel et al. (2007) found an increase in theta power during REM sleep following learning in a non-emotional word pair association task, indicating that REM sleep is also involved in the consolidation of declarative memory for neutral information. However, since there are contradictory findings regarding REM sleep theta in insomnia patients (Merica et al., 1998) and during the first night in a sleep laboratory (Toussaint et al., 1997), further studies are needed to elucidate the precise role played by REM sleep in declarative memory consolidation in disturbed sleep.

Furthermore, the precise role of SWS in declarative memory consolidation is still a matter of debate. While some authors have proposed that SWS has a primary effect on the consolidation process, it is also conceivable that the relationship is indirect (Wilson and McNaughton, 1994; Buzsaki, 1996, 1998; Tononi and Cirelli, 2003, 2006). Instead of promoting declarative memory consolidation directly, SWS may be essential to the normal functioning of other processes that regulate declarative memory consolidation, such as the secretion of cortisol. In accordance with this view, Plihal and colleagues found that declarative memory consolidation was impaired after the administration of cortisol or the glucocorticoid receptor agonist dexamethasone despite comparable proportions of SWS (Plihal and Born, 1999b; Plihal et al., 1999). These results indicate that declarative memory consolidation may depend on the inactivation of glucocorticoid receptors during SWS rather than on the occurrence of SWS itself.

In contrast, neither SWS nor cortisol appeared to have an influence on the overnight consolidation process in our sample. Because our information about HPA axis activity was based on mean cortisol secretion in urine produced from 2000 h to 0700 h, cortisol could have been secreted at any time during any sleep stage within this time frame, and the majority was likely secreted during the cortisol awakening response. Therefore, the influence of cortisol secretion on memory consolidation specifically during SWS cannot be assessed. Interindividual variation in cortisol secretion during SWS may have been diluted by interindividual variation in the amount of cortisol produced at the time of maximal secretion in proximity to waking, thus resulting in comparable total amounts of cortisol. Distinct effects of elevated early or late night cortisol secretion may therefore have been obscured. In patients suffering from major depression, which is a disorder associated with strong hypercortisolism, impaired acquisition has been observed in combination with undisturbed sleep-related declarative memory consolidation (Dresler et al., 2011). Interestingly, the consolidation of procedural memory was impaired in these patients, confirming the results of an earlier study in depressed patients (Dresler et al., 2010b). Because Plihal and colleagues did not find an effect on procedural memory consolidation after administration of cortisol or dexamethason (Plihal and Born, 1999b; Plihal et al., 1999), the role of HPA axis activity in procedural memory consolidation remains unclear. The impairment of procedural memory consolidation observed in multiple sclerosis patients after high-dose corticosteroid therapy, however, has been found to be comparable to that seen in depressed patients (Dresler et al., 2010a). To shed light on the inverse effects of different types of memory consolidation in healthy subjects and patients, corticosteroid levels must be taken into account in further investigations of sleep, HPA axis activity and memory consolidation.

Memory is considered to be a process with different stages, including acquisition, consolidation and retrieval (Müller and Pilzecker, 1900). There is evidence that HPA axis activity can influence memory processing at the stage of acquisition or retrieval: declarative memory performance was observed to be impaired by inducing stress or by pharmacologically increasing cortisol before acquisition (Kuhl-

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mann and Wolf, 2006; Payne et al., 2006, 2007), or before retrieval testing (de Quervain et al., 2000; Wolf et al., 2001; de Quervain et al., 2003; Kuhlmann et al., 2005; Buchanan et al., 2006; Smeets et al., 2008; Tollenaar et al., 2008). In accordance with these results, we observed that cortisol secretion per hour was associated with performance on a word pair association task during acquisition and retrieval testing. Importantly, memory performance during acquisition was in temporal proximity to the circadian nadir of cortisol secretion, and memory performance in retrieval testing was in proximity to the cortisol awakening response peak. The circadian nadir of cortisol and the cortisol awakening response peak represent distinct acute levels of cortisol secretion. Because timed measures of cortisol were lacking, we were unable to establish whether higher levels of total nocturnal cortisol reflected elevated evening cortisol, an exaggerated cortisol awakening response, or both. Further investigations should therefore analyze blood cortisol samples taken at different points over time.

Another limitation is that we cannot rule out an effect of caffeine abstinence on sleep, since subjects were restricted from consuming caffeine after 1200 h on the day they checked into the sleep laboratory for polysomnographic recording. In a systematic review, however, Sin et al. (2009) found that caffeine abstinence improved sleep rather than disturbing it. Furthermore, because the baseline of the task relates to a test after which feedback of the correct answers was given, any improvement on retrieval testing might stem from this feedback and does not necessarily have to be associated with sleep. However, the word pair association task has been used in previous studies with a wake control condition (Gais and Born, 2004; Wilhelm et al., 2008). In these studies, during a retention interval consisting of wakefulness, memory performance either did not improve (Wilhelm et al., 2008) or improved only marginally (Gais and Born, 2004). In contrast, during a retention interval consisting of sleep, memory performance improved three to five times as much as it did during the retention interval consisting of wakefulness. This indicates that while improvement may be attributable in part to feedback, it is due to a much larger extent to sleep. Finally, the one-arm nature of this study means that the associations observed between the variables cannot prove causation.

Taken together, our results provide evidence for the first time that REM sleep may play an important role in declarative memory consolidation in healthy subjects after inducing transient insomnia through the first-night effect. In addition, our results highlight the importance of cortisol secretion in the acquisition and retrieval of word pairs. Further research on sleep and declarative memory should consider sleep macro- and microstructure in addition to memory-relevant biological parameters, such as HPA activity.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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