Effects of Cortisol Suppression on Sleep-Associated Consolidation of Neutral and Emotional Memory

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Background: *Previous research indicates that hippocampus-dependent declarative memory benefits from early nocturnal sleep, when slow-wave sleep (SWS) prevails and cortisol release is minimal, whereas amygdala-dependent emotional memory is enhanced through late sleep, when rapid eye movement (REM) sleep predominates. The role of the strong cortisol rise accompanying late sleep for emotional memory consolidation has not yet been investigated.*

Methods: *Effects of the cortisol synthesis inhibitor metyrapone on sleep-associated consolidation of memory for neutral and emotional texts were investigated in a randomized, double-blind, placebo-controlled study in 14 healthy men. Learning took place immediately before treatment, which was followed by 8 hours of sleep. Retrieval was tested at 11 AM the next morning.*

Results: *Metyrapone suppressed cortisol during sleep and blocked particularly the late-night rise in cortisol. It reduced SWS and concomitantly impaired the consolidation of neutral texts. Emotional texts were spared from this impairing influence, however. Metyrapone even amplified emotional enhancement in text recall indicating amygdala-dependent memory.*

Conclusions: *Cortisol blockade during sleep impairs hippocampus-dependent declarative memory formation but enhances amygdala-dependent emotional memory formation. The natural cortisol rise during late sleep may thus protect from overshooting emotional memory formation, a mechanism possibly pertinent to the development of posttraumatic stress disorder.*

Key Words: Cortisol, emotion, memory consolidation, metyrapone, PTSD, sleep

Sleep represents a biological condition most appropriate for consolidating memories (Gais and Born 2004a; Maquet 2001; Smith 1995; Stickgold et al 2001). In investigations in healthy humans, periods of sleep following learning, compared to wakefulness, consistently enhanced retention of the learned material in a variety of memory tasks. However, different sleep stages seem to be implicated in the process of memory consolidation, depending on the type of memory (Born and Gais 2003; Peigneux et al 2001; Smith 2001). Retention of declarative memory, which includes episodic memory (for events) and semantic memory (for facts), and critically depends on the integrity of the hippocampus (Squire 1992), has been shown to benefit specifically from early nocturnal sleep, in which slow-wave sleep (SWS) predominates (Fowler et al 1973; Plihal and Born 1997); however, when declarative memory for highly emotional rather than neutral material is assessed, the data point to a more beneficial influence of rapid eye movement (REM) sleep, which prevails during the late night (Greenberg et al 1983; Grieser et al 1972; Wagner et al 2001). Emotional forms of memory differ from neutral ones in that the amygdala is critically involved (Cahill and McGaugh 1998; Hamann 2001; Phelps 2004). The amygdala not only mediates simple forms of emotional learning such as fear conditioning but also modulates emotional types of declarative memory (Adolphs et al 1997; Cahill et al 1995; Canli et al 2000; Hamann et al 1999; Pelletier and Pare 2004). Declarative memory for emotional events, although still hippocampus-dependent, becomes specifically enhanced by amygdalar modulation of hippocampal functioning (Akirav and Richter-Levin 2002; Packard and Cahill 2001; Phelps 2004), a mechanism thought to underlie the general finding that emotionally arousing events are better remembered than neutral ones (Cahill and McGaugh 1998; Christianson 1992; Hamann 2001).

Sleep is accompanied by a specific regulation of the release of glucocorticoids (GCs) in humans, mainly cortisol, which are potent modulators of memory functions as well (Lupien and McEwen 1997; Roozendaal 2000, 2002). In humans, GC release is reduced to a minimum during early, SWS-rich sleep, whereas during late sleep, when REM sleep becomes prominent, cortisol levels distinctly increase to reach a maximum at about the time of morning awakening (Born and Fehm 1998). The GCs act on limbic regions including the hippocampus and the amygdala via two receptor types, the high-affinity mineralocorticoid receptors (MRs) and the low-affinity glucocorticoid receptors (GRs; de Kloet et al 1998, 1999). Although the residual GC release during early sleep is sufficient to occupy MRs, the increase in GC release during the late night as well as during stress leads to a predominant activation of GRs. In humans, predominant activation of GRs has generally been found to impair declarative memory formation in neutral standard tasks both during wakefulness and during sleep (Newcomer et al 1994, 1999; Plihal and Born 1999; Plihal et al 1999; Wolkowitz et al 1990). Regarding sleep-associated memory consolidation, enhancing the plasma GC level during early SWS-rich sleep completely blocked any sleep-associated declarative memory formation during this period (Plihal and Born 1999; Plihal et al 1999). Amygdala-dependent emotional memory formation has been shown to benefit from GC increases in studies in awake animals and humans (Abercrombie et al 2003; Buchanan and Lovallo 2001; Cahill et al 2003; Maheu et al 2004; Rimmele et al 2003; Roozendaal 2000, 2002); however, GC effects specifically on sleep-related emotional memory formation have not been investigated.

We examined the role of cortisol for the formation of emotional declarative memory during sleep. Because emotional memory has been found to benefit particularly from REM sleep-rich late sleep, which is a period of high GC release, our interest focused on whether this late night rise in cortisol would support or counteract the formation of emotional memories. For this purpose, we tested the retention of emotional and neutral texts across sleep after blocking nocturnal cortisol synthesis by admin-

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istration of metyrapone, thereby preventing the normal rise in cortisol during late retention sleep.

Methods and Materials

Subjects

Sixteen healthy male students (mean age 24.8 years; mean body mass index 24.4 kg/m^2) with regular sleep–wake rhythms were recruited at the University of Lübeck to participate in the experiments. They were nonsmokers, did not take any medication, and had no history of psychiatric or neurological disorders, sleep or memory disturbances, endocrine dysfunction, or drug abuse. Subjects were acclimated to the experimental sleep condition by spending an adaptation night in the sleep laboratory. On experimental days, they were required to get up before 7 AM, not to take any naps during the day, and to refrain from beverages containing alcohol or (after 3 PM) caffeine. The study was approved by the ethics committee of the University of Lübeck. Subjects were paid for participation and gave written informed consent. Data from two subjects were excluded from analysis because of an enduring stress response to venipuncture, leading to evening plasma cortisol levels > 14 μg/dL at learning. Thus, the final sample included 14 subjects.

Design and General Procedure

The study followed a randomized, double blind, placebo-controlled crossover design. The two experimental nights for each participant (metyrapone vs. placebo, with the order balanced across subjects) were separated by at least 1 week. Each night started at 9:30 PM with placement of a venous catheter for blood collection into the forearm and subsequent attachment of electrodes for polysomnographic recordings. The subject then performed the memory tasks (learning phase, 10:30–11:30 PM; see below). Metyrapone (3 g) or placebo was administered orally immediately before subjects went to bed at midnight to allow 8 hours of sleep (midnight to 8 AM) for memory consolidation. The capsules were administered with milk to prevent possible adverse side effects of metyrapone treatment. Only two subjects reported slight, short-term side effects (nausea). Because glucocorticoids can affect memory performance by influencing not only consolidation but also retrieval (de Quervain et al 2000), retrieval testing took place between 11 AM and 12 noon, when cortisol suppression by metyrapone had ceased. In the interval between awakening (8 AM) and retrieval, subjects stayed at the laboratory to engage in standardized low-arousal activities (playing simple games with the experimenter, watching films with low emotional impact). A light breakfast was served in the morning. Blood was sampled before and after learning and retrieval, respectively, and at half-hour intervals between these phases to determine plasma concentrations of cortisol, corticotropin (ACTH), and norepinephrine (NE). During sleep, blood was collected via a long plastic tube from an adjacent room, leaving the subjects' sleep undisturbed.

Memory Testing

To assess emotional versus neutral memory, standardized German texts were used (Schürer-Necker 1994) for which sleep-associated consolidation has been demonstrated (Wagner et al 2001). The material comprised two parallel texts in each category (emotional: "Paraplegia" and "Murderer"; neutral: "Bronze" and "Fashion") to allow an assessment on two experimental occasions in each subject. Differential affective impact of emotional vs. neutral texts had been confirmed by both subjective and physiologic measures (Schürer-Necker 1994; Wagner et al 2001). Of the emotional texts, "Paraplegia" was a report of a paraplegic man describing frankly his handicapped situation, including sexual problems. "Murderer" described in detail the killing procedures of a murderer of children. Of the two neutral texts, "Bronze" dealt with the manufacture of a bronze sculpture, "Fashion" with clothing presented on a fashion show. Texts were roughly matched in length (between 202 and 255 words). Expressed in the number of content words (nouns, adjectives, and verbs), which was used for memory assessment (described later), the average length was 95.0 for the neutral texts ("Bronze," 78, "Fashion," 112), and 94.5 for the emotional texts ("Murderer," 94, "Paraplegia," 95). Four additional neutral texts served as primacy and recency buffers. Thus, in the learning phase of each experimental night subjects learned two experimental texts (one emotional and one neutral), embraced by two buffer texts not included in the analyses. The order of the experimental texts within a session and of parallel versions on the subject's two test occasions was balanced across subjects.

The subject was instructed to read the texts, printed on a sheet of paper, thoroughly within 4 min (which was abundant time) and to memorize as many details as possible for later recall. He was informed that recall was tested immediately after reading and again after retention sleep. After reading subjects first rated each text on 7-point scales (−3 to 3) with regard to the following dimensions: comprehensible–uncomprehensible, interesting–uninteresting, difficult–easy, neutral–emotional, harmless–startling, important–unimportant, vivid–abstract, amusing–serious, boring–arousing, familiar–unfamiliar, positive–negative. Thereafter, immediate free recall was tested to determine the original encoding level. Subjects were asked to write down the previously read text as exactly as possible, ideally in a literal way. No time limit was set. Retrieval testing after retention sleep was performed in the same manner. No restriction was given concerning the order of text retrieval. The only constraint was that information from different texts had to be written on separate sheets of paper.

Assessment of memory performance was based on the number of content words (nouns, adjectives, and verbs) correctly recalled. Validity of this measure was confirmed by comparisons to other measures (including complex measures relying on propositions and semantic relations between words) in previous experiments (Schürer-Necker 1994). Apart from words exactly reproduced, synonyms as well as word type transitions (e.g., from noun to adjective) were also considered correct if both words were derived from the same word stem.

At learning and at retrieval testing, recall performance was determined by the percentage of text content words correctly recalled. To assess memory retention as an estimate of consolidation between learning and retrieval, the percentage of content words recalled at retrieval was calculated with reference to performance at learning, which was set to 100%. Representing basically a declarative task, memory formation for emotional texts relies not only on the amygdala involved specifically in emotional memory functions, but also on the hippocampus-dependent declarative memory system. To separate emotional aspects of memory consolidation from declarative memory function, we determined additionally in each learning and retrieval phase from the individual recall data the extent of amygdala-mediated emotional enhancement of declarative memory as the relative superiority (percent gain) of emotional compared to neutral text recall (Cahill and McGaugh 1998; Christianson 1992; Hamann 2001; Phelps 2004). Also for this measure of "pure" emotional memory a retention score was determined across the

consolidation interval, that is, the change from learning to retrieval.

As a test of specificity of results, subjects also performed a procedural memory task of mirror tracing that did not rely on hippocampal or amygdalar function (Laforce and Doyon 2002). In this task, described previously in detail (Plihal and Born 1997), subjects had to trace six figures that they saw only through a mirror, as fast and as accurately as possible, at learning and at retrieval testing. Performance measures were draw time (time needed for completion of a figure) and error count (number of deviations from the path), averaged across the six figures. Parallel versions of the task were used on the two nights. At learning, subjects were first trained by tracing a simple star-shaped figure until they reached a criterion of < 6 errors. Task order was fixed, with texts always preceding mirror tracing.

At the beginning of each learning and retrieval phase, mood was assessed by self-ratings on 5-point scales of drowsiness, activation, tension, tiredness, boredom, motivation, and concentration. This was followed by a short test of attentional capacity (Wagner et al 2001) consisting of 60 simple arithmetical tasks (addition and subtraction), which had to be solved as quickly and accurately as possible. To control for memory effects specifically related to retrieval rather than consolidation (de Quervain et al 2000), a test of fluency in word retrieval from semantic memory was performed immediately before free text recall in the retrieval phase (Regensburger Wortflüssigkeitstest [RWT; Aschenbrenner et al 2000], a German adaptation of a test originally developed by Christensen and Guilford [1958]).

Sleep Recordings, Hormone Assays, and Statistical Analysis

Sleep was assessed by standard polysomnographical recordings, which were scored offline by two experienced raters according to the criteria by Rechtschaffen and Kales (1968). For each night, total sleep time, sleep onset latency, and absolute as well as relative time spent awake and in sleep stages 1, 2, 3, 4, and REM sleep were determined. To calculate SWS, the sum of time in stage 3 and 4 sleep were used. Sleep parameters were determined for the whole night and separately for the first and second half.

Blood samples were immediately centrifuged and then stored at –20°C until analysis by chemiluminescent immunoassay (Immulite system, DPC Biermann, Bad Nauheim, Germany) for determination of serum cortisol (sensitivity, .2 μg/dL; inter- and intraassay coefficient of variation < 10%) and plasma ACTH (sensitivity, 10 pg/mL; inter- and intraassay coefficient of variation < 10%), and by high-performance liquid chromatography for determination of plasma NE (sensitivity 9 pg/mL; interassay coefficient of variation 6.1%). For analysis, hormone levels were collapsed across five relevant time intervals: learning (10:30–11:30 PM), early sleep phase (12 midnight–4 AM), late sleep phase (4 AM–8 AM), morning phase (8–11 AM), and retrieval (11 AM–12 noon).

Statistical analysis was performed by analyses of variance (ANOVA) with the two repeated-measures factors of treatment (metyrapone vs. placebo) and emotionality (neutral vs. emotional text) for memory variables, and the two repeated-measures factors of treatment (metyrapone vs. placebo) and time (5 intervals) for hormone levels. Significant effects in the ANOVA were specified by pairwise contrasts using *t* tests. Likewise, ANOVA with subsequent pairwise comparisons was used to determine differences between conditions in sleep, cortisol, and control variables of text ratings, mood, attentional capacity, and retrieval abilities. Degrees of freedom were corrected after Greenhouse–Geisser. The significance level was set to $\alpha = .05$.

Results

Hormones and Sleep

Cortisol concentrations were comparable between conditions at learning but were strongly suppressed overnight after administration of metyrapone (Figure 1). The suppression was already effective during early sleep ($p < .01$) and reached its maximal extent during late sleep, when the normal nocturnal rise in cortisol, as observable in the placebo condition, was actually prevented [1.3 ± .2 vs. 12.5 ± .7 μg/dL, $t(13) = -16.85$, $p < .0001$]. In the morning hours after awakening, cortisol gradually increased in the metyrapone condition to return to placebo levels at the time of retrieval ($p > .20$). Corticotropin increased in

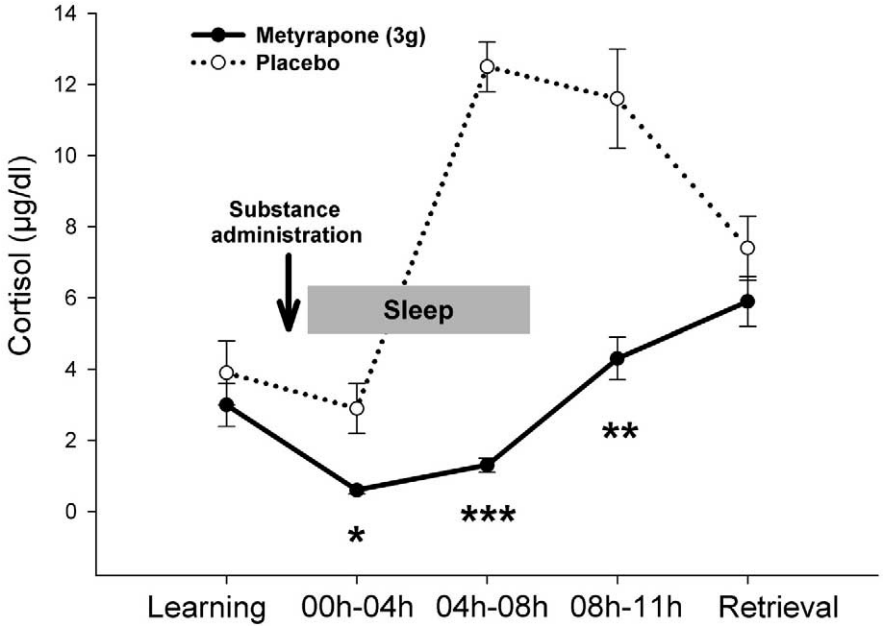

Figure 1. Cortisol concentrations during five relevant time intervals. Metyrapone, administered after learning immediately before 8 hours of retention sleep, began to suppress cortisol during early sleep (midnight–4 AM) and completely blocked the normal rise in cortisol during late sleep (4–8 AM). Cortisol levels after metyrapone normalized by the time of retrieval (11 AM–noon). *$p < .01$. **$p < .001$. ***$p < .0001$.

Table 1. Concentrations of ACTH and Norepinephrine

	Placebo		Metyrapone			
	Mean	SEM	Mean	SEM	*t*	*p*
ACTH (pg/mL)						
Learning	6.7	.6	6.3	.7	−.70	
Early sleep	7.5	.8	28.6	9.5	2.22	<.05
Late sleep	27.1	2.9	173.4	33.3	4.59	<.001
Morning	17.6	2.6	291.8	43.9	6.30	<.001
Retrieval	12.8	1.6	233.5	45.2	4.94	<.001
Norepinephrine (pg/mL)						
Learning	102.0	21.2	122.5	32.0	.97	
Early sleep	62.7	10.9	74.6	12.8	1.74	
Late sleep	67.1	13.7	71.8	14.3	1.11	
Morning	127.0	28.7	121.1	27.5	−.53	
Retrieval	132.8	28.8	160.0	33.2	1.72	

Blood hormone concentrations for the five time intervals of interest. ACTH: corticotropin.

response to metyrapone-induced suppression of cortisol (Table 1, upper panel). This increase developed in the early night ($p = .047$) and levels remained distinctly elevated throughout the subsequent intervals ($p < .001$). Norepinephrine levels generally dropped during the night after learning and then increased again after sleep (Table 1, lower panel). This time course was independent of metyrapone treatment ($p > .25$, for treatment × time interaction).

Sleep data are presented in Table 2. Metyrapone markedly reduced SWS (on average by 18.8%; $p < .01$), whereas there was a concomitant trend toward increased stage 1 sleep ($p < .10$). Separate analyses of the two halves of the night revealed that both the decrease in SWS and the increase in stage 1 sleep after metyrapone were confined to early sleep, whereas late sleep was virtually unaffected by metyrapone (Table 2). No other sleep parameter was affected by metyrapone in the early, late, or whole sleep period. In particular, metyrapone did not cause any change in REM sleep.

Emotional and Neutral Memory

Memory data are summarized in Table 3. As expected, immediate recall at learning before treatment did not differ between conditions ($p > .40$, for all comparisons). Critical for the assessment of memory consolidation (as opposed to presleep learning and retrieval) were the retention measures, that is, changes across the treatment-associated period of sleep. Retention of neutral versus emotional memory was differentially affected by metyrapone (Figure 2, left panel). Metyrapone treatment significantly diminished retention of neutral texts in comparison to placebo ($p = .019$), whereas retention of emotional texts was comparable for both treatment conditions [$p = .60$; $F(1,13) = 8.56$, $p = .012$ for treatment × emotionality interaction]. In the metyrapone condition, retention of emotional texts was significantly superior to that of neutral texts ($p = .02$; Figure 2, left panel).

The fact that memory for the emotional texts was spared from the metyrapone-induced impairment, although sharing aspects

Table 2. Sleep Measures

	Placebo		Metyrapone			
Sleep Parameter	Mean	SEM	Mean	SEM	*t*(13)	*p*
Total Night						
Sleep onset (min)	10.4	2.3	9.1	3.0	−.37	
Sleep time (min)	471.6	2.2	469.9	4.0	−.47	
Wake (%)	1.2	.1	1.8	.5	1.13	
S1 (%)	5.2	1.3	9.6	2.2	1.90	<.10
S2 (%)	52.5	1.7	52.1	1.9	−.22	
SWS (%)	17.6	1.6	14.3	1.0	−3.32	<.01
REM (%)	22.8	1.0	21.2	1.0	−1.12	
Early Night						
Wake (%)	1.5	.3	2.5	1.0	.91	
S1 (%)	3.7	1.2	10.9	2.3	3.73	<.01
S2 (%)	53.3	3.1	54.1	2.2	.27	
SWS (%)	29.7	3.0	21.5	1.8	−3.27	<.01
REM (%)	11.3	1.1	9.9	1.4	−.74	
Late Night						
Wake (%)	1.2	.1	1.1	.1	−.79	
S1 (%)	6.7	2.2	8.3	2.6	.48	
S2 (%)	51.6	2.5	50.1	2.7	−.48	
SWS (%)	5.5	1.4	7.1	1.5	.92	
REM (%)	34.3	2.1	32.4	1.7	−.81	

S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow-wave sleep; REM, rapid eye movement sleep.

Table 3. Memory

	Placebo		Metyrapone			
	Mean	SEM	Mean	SEM	$t(13)$	p
Text Memory						
Learning						
Neutral text recall	27.9	3.1	30.6	2.9	.86	
Emotional text recall	49.6	4.2	52.3	2.9	.57	
Emotional enhancement (% gain)	101.6	23.2	106.8	39.4	.11	
Retrieval						
Neutral text recall	26.2	2.9	25.3	3.1	−.30	
Emotional text recall	45.0	4.4	46.9	3.9	.38	
Emotional enhancement (% gain)	90.6	22.3	139.6	58.6	.82	
Retention						
Neutral texts (% of learning)	96.7	6.2	80.7	3.5	−2.67	<.05
Emotional texts (% of learning)	90.6	3.8	88.1	4.0	−.54	
Emotional enhancement (difference to learning)	−11.0	10.3	32.8	19.9	2.45	<.05
Mirror Tracing						
Learning						
Draw time (sec)	68.8	9.3	56.6	5.1	−1.09	
Error count	7.7	1.8	7.9	2.9	.07	
Retrieval						
Draw time (sec)	48.0	3.0	45.9	3.1	−.69	
Error count	4.3	.8	5.1	1.5	.82	
Retention						
Draw time (% of learning)	78.8	5.4	83.0	2.7	.58	
Error count (% of learning)	80.0	12.2	78.0	8.1	−.12	

Text recall at learning and retrieval is indicated with reference to text length. Retention refers to the change from learning to retrieval. Emotional enhancement, as a measure of specifically amygdala-related memory formation independent of hippocampal function is calculated at learning and retrieval as ((Emotional text recall / Neutral text recall) * 100) − 100, indicating a percent gain value. Retention of neutral and emotional texts is given in percent values in relation to learning performance and as difference in the scores at retrieval minus learning for the emotional enhancement (because this is already a percent value).

of hippocampus-dependent declarative memory with the neutral texts, points to a separate enhancing influence of metyrapone on aspects of emotional memory formation compensating for the weakened declarative text memory. This was evident through an additional analysis on the emotional enhancement of declarative memory defined by the superiority (in percent) of recall of emotional over neutral texts, serving as an estimate of the purely emotional aspects of memory formation. The emotional enhancement was indeed significantly increased across retention sleep after metyrapone treatment compared with placebo [metyrapone, 32.8 ± 19.9% vs. placebo, −11.0 ± 10.3%, $t(13) = 2.45$, $p = .029$; Figure 2, right panel]. Procedural memory for mirror tracing skills remained completely unaffected by metyrapone treatment with respect to both speed and accuracy (Table 3).

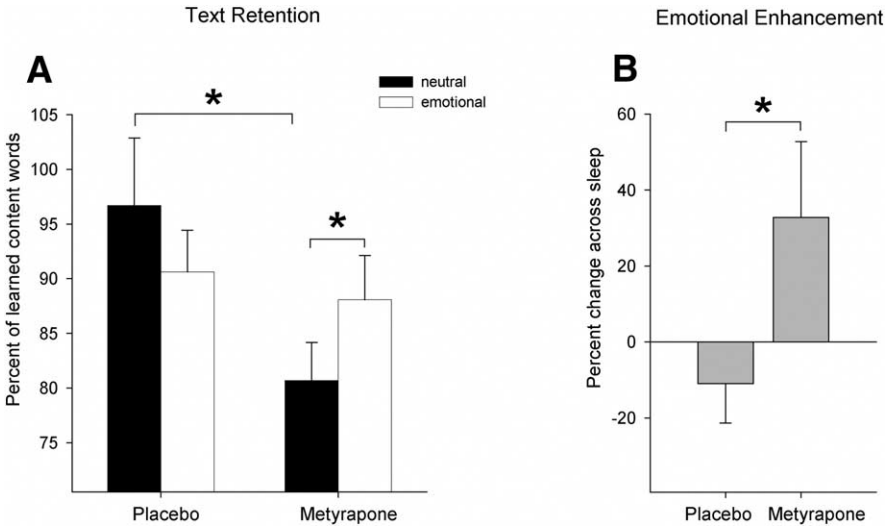

Figure 2. Metyrapone effects on memory retention across sleep. **(A)** Compared to placebo, metyrapone reduced retention of neutral texts but left retention of emotional texts undisturbed. **(B)** Emotional enhancement (relative superiority of emotional over neutral text recall), serving as a "pure" measure of emotional memory (independent of hippocampal function), was increased after metyrapone compared with placebo. *$p < .05$.

Text Ratings, Retrieval Abilities, Attentional Capacity, and Mood

Confirming the validity of the material, emotional compared with neutral texts were rated on a highly significant level as more startling (2.07 ± .18 vs. −2.14 ± .26), more emotional (1.64 ± .25 vs. −1.36 ± .24), more negative (−1.96 ± .21 vs. .46 ± .30), more arousing (.61 ± .24 vs. −1.61 ± .20), and more serious (2.11 ± .21 vs. .29 ± .26); all Fs(1,13) > 30, $p < .0001$. To a lesser degree, emotional texts were also judged as more interesting (.79 ± .26 vs. −.75 ± .27), more important (.43 ± .29 vs. −1.64 ± .27), more comprehensible (2.00 ± .26 vs. −.25 ± .47), and less difficult (−.64 ± .34 vs. .75 ± .24); all Fs(1,13) > 10, $p < .01$. Emotional and neutral texts did not differ in ratings of familiarity and vividness.

Metyrapone did not influence general retrieval abilities, as assessed by the word fluency test in the retrieval phase [metyrapone 54.4 ± 3.2 vs. placebo 52.1 ± 2.7 items retrieved, $t(13)=1.15$; $p = .27$], nor did it affect scores of attentional capacity [145.1 ± 9.9 vs. 147.9 ± 12.7 sec, $t(13) = -.56$, $p = .58$]. Ratings of subjective mood at retrieval appeared to point towards slightly reduced mental vigor after metyrapone compared to placebo on some scales (drowsiness, 2.21 ± .24 vs. 1.93 ± .25; activation, 3.07 ± .20 vs. 3.50 ± .25; tension, 1.93 ± .17 vs. 2.21 ± .21; concentration, 3.07 ± .17 vs. 3.36 ± .17). The difference reached statistical significance only for the activation rating, however ($p < .05$). There were also no statistical differences in tiredness (2.21 ± .32 vs. 2.21 ± .31), boredom (2.86 ± .29 vs. 2.93 ± .31), and motivation (3.36 ± .17 vs. 3.50 ± .17).

Discussion

This study investigated in healthy humans effects of overnight suppression of cortisol by metyrapone on sleep-related consolidation of emotional and neutral declarative memory, using text materials. The primary finding is that metyrapone reduced consolidation of the neutral texts but left consolidation of emotional texts intact. To dissect the amygdala-dependent emotional contribution from hippocampal function in memorizing the emotional texts, we determined in a supplementary analysis the emotional enhancement in memory, that is, the relative superiority of emotional over neutral text recall. Enhancement in declarative memory for emotionally arousing compared with neutral material is a consistent finding in human studies, which has been shown in many clinical and neuroimaging studies to depend on the amygdala (Adolphs et al 1997; Cahill et al 1995; Canli et al 2000; Hamann et al 1999). In this study, we found emotional enhancement to be substantially elevated across retention sleep after metyrapone compared with placebo. Our results thus indicate that overnight cortisol suppression by metyrapone exerts a general detrimental effect on hippocampus-mediated memory for texts. It appears, however, even to enhance the specific amygdala-mediated emotional memory function, with this effect compensating for the weakened text memory in the case of emotional texts. Specificity of these influences was confirmed in a procedural control task of mirror tracing skills. In this task, which relies neither on the hippocampus nor the amygdala, metyrapone did not affect memory formation.

The process of memory formation can be divided into three stages: acquisition, consolidation, and retrieval. The focus here was on memory consolidation (McGaugh 2000), the time-consuming process of strengthening memory representations, which is known to be supported by sleep (Gais and Born 2004a, 2004b; Maquet 2001; Smith 1995; Stickgold et al 2001; Wagner et al 2004). Glucocorticoids play a modulating role in all three subprocesses (de Quervain et al 2000; Lupien and McEwen 1997). Therefore, here metyrapone was administered postlearning, excluding a treatment effect on acquisition. Moreover, the study design ensured that cortisol suppression had terminated at the time of retrieval testing. Accordingly, cortisol suppression was in fact only effective during consolidation. An influence on retrieval was likewise excluded because of the lack of differences between treatment conditions in our control task aimed specifically at assessment of retrieval operations. Moreover, influences due to unspecific effects of metyrapone on attentional capacity or subjective mood are unlikely because respective scores were not substantially affected by metyrapone.

The general impairing effect of metyrapone on hippocampus-dependent memory consolidation in this study may result from changes in the sleep architecture. Consistent with earlier findings (Jahn et al 2003; Neylan et al 2003), metyrapone reduced SWS, which was partly compensated for by increased amounts of light stage 1 sleep. These effects were confined to the first half of sleep, in which most of nocturnal SWS takes place. During early sleep, the amount of SWS was reduced by about 30%. With the background of data pointing to a specific beneficial function of SWS in the consolidation of hippocampus-dependent declarative memory (Born and Gais 2003; Fowler et al 1973; Plihal and Born 1997; Smith 2001), this form of memory may have generally suffered from SWS reduction in the early night after metyrapone treatment.

Also, impairment of declarative memory may reflect a direct consequence of cortisol suppression by metyrapone, which, although most pronounced in the late night, was already effective during the early night. This explanation seems surprising at first glance, because low cortisol levels and low occupation of GRs during the early night have been found to be a prerequisite for beneficial effects of sleep during this period on declarative memory (Plihal et al 1999; Plihal and Born 1999). If cortisol at this time of the circadian nadir is further reduced, however, this also represents a condition of disturbed balance in corticosteroid receptor occupation, because MRs, 70%–80% of which are normally bound even at the time of the cortisol nadir (de Kloet et al 1998), are not sufficiently activated. Thus, rather than a hyperactivation of GRs, in this case the reason for the disturbance is a hypoactivation of MRs. This interpretation is in line with previous studies that similarly showed impairing effects of metyrapone on declarative memory during wakefulness in young and aged humans (Lupien et al 2002a, 2002b; Maheu et al 2004). Notably, activation of MRs has been consistently found to enhance and prolong long-term potentiation (LTP) in hippocampal neurons, a synaptic mechanism considered to underlie memory formation (Korz and Frey 2003; Pavlides and McEwen 1999). Insufficient MR occupation after metyrapone-induced cortisol suppression could thus explain the substantial impairment of hippocampus-dependent memory formation in our subjects. This interpretation also agrees with the generally observed inverted U-shape function for the dose–response relationship between GCs and cognition, with both too high and too low levels of circulating GCs exerting detrimental effects by shifting the GR:MR occupation ratio away from the optimal balance (Belanoff et al 2001; de Kloet et al 1999; Lupien and McEwen 1997).

Interestingly, emotional text memory was spared from the impairing effects of cortisol suppression by metyrapone. The critical difference between neutral and emotional text memory is

that while both are hippocampus-dependent, only the latter additionally involves a modulating action of the amygdala on hippocampal memory formation. Although we did not assess brain imaging data in this study and did not distinguish between memories for gist and for detail as has been done by others (e.g., Adolphs et al 2005; Heuer and Reisberg 1990), the same differential involvement of the amygdala in neutral versus emotional memory formation as revealed consistently in a variety of neuroimaging and clinical studies likewise using declarative tasks can also be assumed here (for overviews, see Hamann 2001; Phelps 2004). In fact, the general superiority of emotional compared with neutral text recall ("emotional enhancement") assumed to result primarily from amygdala involvement in declarative memory was confirmed. On average, subjects recalled about twice as much of the emotional as the neutral texts. Importantly, this emotional enhancement, as a measure reflecting most purely amygdala-dependent emotional memory formation, was even further increased by metyrapone across consolidation sleep. In the case of the emotional texts, this strengthening of amygdalar memory formation fully compensated for the parallel impairment of hippocampal function.

We have previously shown that emotional memory is particularly facilitated by late, REM sleep-dominated sleep, which increases emotional reactivity to previously seen aversive pictures and enhances emotional compared with neutral declarative memory for texts (Wagner et al 2001, 2002), effects that fit well to neuroimaging findings of enhanced amygdala activation during REM sleep (Maquet et al 1996; Nofzinger et al 1997). On this background, the physiologic conditions in the second half of the night, where REM sleep prevails, appear to be most critical for the findings on amygdala-dependent emotional memory here. Although metyrapone left sleep in the late night entirely undisturbed (and in particular had no effect on REM sleep), it simultaneously exerted maximal cortisol suppression and completely blocked the circadian rise in cortisol normally occurring at this time. The finding of increased emotional enhancement after metyrapone thus excludes the possibility that the normally high cortisol level during late sleep serves as a prerequisite for emotional processing during concomitant periods of REM sleep. On the contrary, this late night rise in cortisol appears to dampen amygdala-dependent emotional processing and could thus exert a protective function by preventing excessive emotionality in memory. This outcome, in line with recent findings in animals (e.g., Wang et al 2003), suggests that the specific interaction between REM sleep and the release of stress hormones during postlearning sleep is most critical for the consolidation of emotional memories.

Our finding of a facilitating role of low cortisol levels in amygdala-dependent emotional memory formation seems to be in contrast with previous animal and human studies indicating supportive effects of GCs on emotional memory (Abercrombie et al 2003; Buchanan and Lovallo 2001; Maheu et al 2004; Roozendaal 2000). None of these former studies, however, specifically referred to memory formation during sleep, which, as an "offline" brain state characterized by downregulated sensory input, underlies qualitatively different physiologic mechanisms than wakefulness (Stickgold et al 2001). Moreover, in almost all previous human studies, drugs were administered prelearning, which makes a direct comparison with the present study difficult. Only postlearning drug administration, as applied here, allows a selective manipulation of the consolidation phase of memory without affecting acquisition.

Although we have focused on the well-known role of the amygdala in emotional processing here, the contribution of metyrapone effects on other relevant GC target regions in the brain cannot be excluded, although little is known about mechanisms of emotional memory formation unrelated to amygdala functions. It is also to be considered that effects of metyrapone could be mediated by endocrine changes secondary to cortisol suppression. Most important, metyrapone strongly elevates levels of corticotropin releasing hormone (CRH) and ACTH due to the lacking hypothalamo-pituitary feedback inhibition. Specifically, although there are no hints at strong memory modulating effects of ACTH (Born et al 1986), animal models point to an enhancing role of CRH in amygdala-mediated emotional reactivity and learning (Heilig et al 1994; Roozendaal et al 2002; Steckler and Holsboer 1999). Such influences could have contributed to the memory effects of metyrapone on emotional versus neutral texts in our study. Norepinephrinergic activity is also known to contribute to emotional memory formation (McGaugh 2000; Southwick et al 2002). In line with previous findings in humans (Del Corral et al 1998), however, metyrapone did not change blood concentrations of NE significantly in our subjects.

From a clinical perspective, the results of our study seem to be particularly pertinent to the mechanisms in posttraumatic stress disorder (PTSD), a mental disorder with primary symptoms of hyperemotionality in memory, as reflected by intrusive memories, flashbacks, and nightmares (Charney et al 1993; Pitman 1989; vanOyen 1997; Yehuda 2002). These symptoms are thought to result from enhancement of amygdala-mediated memory processing in combination with impaired hippocampal functioning (Elzinga and Bremner 2002; van der Kolk 1994; Yehuda 2002). In fact, neuropsychologic testing of PTSD patients typically reveals impairment in standard tasks of declarative memory (Barrett et al 1996; Elzinga and Bremner 2002; Sapolsky 2000; Vasterling et al 1998), whereas emotional (trauma-related) material is often well remembered (Golier et al 2003; McNally 1998). Interestingly, reduced basal cortisol levels are a frequently encountered condition in PTSD (Kanter et al 2001; Mason et al 1986; Rohleder et al 2004; Yehuda et al 1990, 1995), and 24-hour profiles have shown that during sleep this cortisol reduction is particularly pronounced in the second half of the night (Yehuda et al 1996). Moreover, sleep disturbances are one of the diagnostic criteria of PTSD (American Psychiatric Association 1994), and in particular reductions of SWS have been observed in PTSD patients in several studies (Fuller et al 1994; Glaubman et al 1990; Neylan et al 2003). Thus, our experiments provide a useful model for several features inherent in PTSD and suggest that reduced cortisol levels, especially during sleep, play a crucial role for the development of "overconsolidation" (Pitman 1989) of emotional memories in this disease. Interestingly, recent findings have demonstrated that cortisol administration can alleviate symptoms of traumatic memories in PTSD patients (Aerni et al 2004). Moreover, as a prevention strategy, the administration of stress doses of cortisol for several days in survivors of hyperdynamic septic shock or perioperatively in patients undergoing cardiac surgery reduced the probability that these patients developed symptoms of PTSD (Schelling et al 2001, 2004). The results of our study suggest that these therapeutic effects are primarily due to the dampening influence of elevated cortisol levels on the consolidation of emotional memories, particularly during sleep.

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