

Effects of Total Sleep Deprivation in Major Depression: Overnight Improvement of Mood is Accompanied by Increased Pain Sensitivity and Augmented Pain Complaints

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Objective: Major depressive disorder (MDD) is associated with more pain complaints and an altered pain perception. Studies regarding the longitudinal relationship between depressive symptoms and pain processing have rarely been performed and have produced inconsistent results. To clarify how short-term alleviation of depressive mood is linked to changes in pain processing, the effect of sleep deprivation (SD) on pain and somatosensory thresholds, pain complaints, and mood was investigated in MDD patients. **Methods:** Nineteen drug-free inpatients with Diagnostic and Statistical Manual of Mental Disorders, fourth edition, diagnosis of MDD were investigated for 3 weeks. All patients received cognitive-behavioral therapy and were randomized to obtain either additional SD therapy (six nights of total SD, separated by recovery sleep) or no SD therapy (control group). Heat/cold pain thresholds, warmth/cold thresholds, measures of current pain complaints, and mood were assessed the evening before and the morning after SD as well as before and after a normal night sleep in the control group. Long-term changes of depressive symptomatology were assessed by weekly mood ratings. **Results:** Both treatment groups improved markedly in mood over the 3-week treatment period. SD regularly induced a moderate but statistically nonsignificant overnight improvement of mood, which was abolished by recovery sleep. Compared with the control condition, SD significantly decreased heat pain thresholds and nearly significantly cold pain thresholds; SD significantly augmented pain complaints the next morning. No such effects were observed for somatosensory thresholds. **Conclusions:** SD induced differential short-term effects on mood and pain, with the patients being less depressed but more pain vulnerable. **Key words:** depression, pain, sleep deprivation.

MDD = major depressive disorder; **SD** = sleep deprivation; **CDT** = cold detection threshold; **WDT** = warmth detection threshold; **CPT** = cold pain threshold; **HPT** = heat pain threshold; **BDI** = Beck Depression Inventory; **HDRS** = Hamilton Depression Rating Scale; **ANOVA** = analysis of variance; **GG** = Greenhouse-Geisser; **D-S** = Depression Scale; **Bf-S** = Scale of Well-Being.

INTRODUCTION

Previous research has shown that depression is associated with an increased frequency of pain complaints (1). Almost half the depressive patients also experience pain (2). Furthermore, the severity of pain complaints in depression was found to predict a longer time to remission (3). Although most studies have focused on the expression of spontaneous pain (clinical pain complaints), only a few studies have examined pain sensitivity in depression. Paradoxically, the majority of these studies revealed a decreased sensitivity to noxious stimuli in depressive patients compared with healthy controls (4). The rare findings of increased pain sensitivity in depression seem to depend on specific stimulus characteristics. Patients with a major depression showed an increased responsiveness during ischemic muscle pain whereas pain sensitivity to heat and electrical stimuli remained decreased (5). These results are partially compatible with the hypothesis that patients with depression show a decreased response to

phasic cutaneous pain stimuli whereas increased pain responsiveness seems to result from the application of tonic deep somatic stimuli (6). However, the mechanisms involved in altered pain sensitivity in depression, especially considering the findings of a decreased response to noxious stimulation, and its relationship to increased clinical pain are still unclear.

The next step to be taken is the comprehensive and precise description of the relationship between pain processing (i.e., pain sensitivity and spontaneous pain) and the core symptoms of depression (7). In cross-sectional studies only weak correlations between measures of depressive symptomatology and pain sensitivity have been reported (5,8). The evidence from longitudinal studies is still preliminary. Von Knorring (9) suggests that lowered responsiveness to electrical pain stimuli during the acute stage of the disease tends to normalize after clinical recovery. A relationship between the core symptoms of depression and pain sensitivity was also found by a study of Schreiber et al. (10), in which an electroconvulsive treatment decreased severity of depression and increased pressure pain as well as pressure pain tolerance thresholds. This result is in contrast to the study of Gormsen et al. (11), which demonstrated significant mood improvements after electroconvulsive treatment without an altered sensitivity to noxious pressure and thermal stimuli. Bär et al. (12) observed a low responsiveness to heat pain stimuli in patients with depression during the initial stage of treatment with antidepressants as well as after recovery. Taken together, there are inconsistent findings regarding the time-course of pain sensitivity during clinical improvement of depression. The heterogeneity of the results may be due to methodological differences, such as sample selection criteria, methodology of pain threshold assessments, the kind of antidepressant treatment, or marked variations in the observation period ranging from 4 weeks (10) to 7 months (12). However, a common characteristic of these studies is that they focused primarily on long-term changes in mood and pain, especially under treatment with antidepressant agents.

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To our knowledge, no study has yet investigated whether and how an altered pain sensitivity in depression is linked to short-term variations of mood, which can occur spontaneously, for example by circadian rhythmicity (13) or day-to-day fluctuations (14), but also in response to certain antidepressant treatment strategies.

One of the most effective short-term treatments in depression is sleep deprivation (SD) with a response rate of 40% to 60%, but the antidepressant effect of SD is only a transient one because a relapse into depression usually occurs after one night of recovery sleep or short daytime naps (for a review, see (15)).

The main objective of the present study was to investigate the short-term effects of SD on the core symptoms of depression and pain processing. Assuming that—based on previous findings—patients with depression seem less sensitive to phasic experimental pain and that this altered pain sensitivity is state-dependent and closely linked to the affective symptoms, we hypothesized that SD produces a rapid affective amelioration, accompanied by a normalization of pain sensitivity (i.e., an increase in pain responsiveness). In considering the expected relapse into mood deterioration after recovery nights (nights without SD), we further hypothesized that the effects of SD on pain sensitivity are annulled by recovery nights. In addition to the measurement of pain sensitivity under conditions of SD therapy, current pain complaints were assessed to clarify the nature of the relationship between pain sensitivity and spontaneous pain in patients with depression. Furthermore, somatosensory thresholds were assessed to test the specificity of the hypothesized changes in pain.

The procedure of SD treatment applied included a total of six nights of SD separated by two or three nights of undisturbed sleep, which allowed for assessing the reliability of the short-term effects of SD and recovery. Because SD therapy was implemented in an intensive cognitive behavioral treat-

ment program lasting 3 weeks, a secondary aim of the study was to investigate the affective and pain symptoms in the time-course of a treatment known for long-term effects.

METHODS

Subjects

Twenty inpatients with a current Major Depressive Disorder (MDD) with either a single or a recurrent episode according to the Diagnostic and Statistical Manual of Mental Disorders criteria (7) participated in the study, which was conducted between October 2000 and September 2004. They were recruited from consecutively admitted patients for hospital treatment. To obtain a reliable diagnosis of a MDD and of other concomitant mental disorders, each patient was interviewed by an experienced psychiatrist, who used the German version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (16). Patients with a comorbid axis-I or axis-II disorder were excluded from study participation. Furthermore, suicidal tendencies before or during the study period as well as any change of diagnosis during inpatient treatment led to exclusion. Further exclusion criteria were neuropathies, disk diseases, nerve injuries at the upper extremities, endocrine disorders, dermatosis at the upper extremities, pregnancy, and shift work within 3 months or transmeridian travel within 1 month before the study. All patients were studied drug free. In case of prior medications, there was a minimal 6-day washout period, the exact duration of which was at least three times the half-life of the respective drug and its active metabolite. One patient withdrew from the study after 1 week and was excluded from statistical analyses.

Table 1 shows the major clinical characteristics of the remaining 19 patients. The ethics committee of the medical faculty of the University of Marburg, Germany, approved the protocol; all patients gave written, informed consent.

Experimental Protocol

General Design

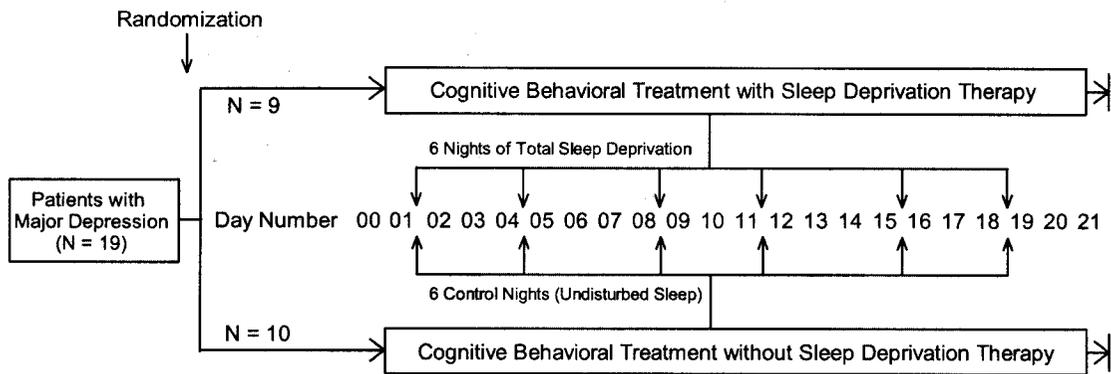
Each study patient received an intensive (five sessions weekly) manualized treatment (17), consisting of behavioral activation, cognitive restructuring, and social skills training. In addition, the patients were randomly assigned to either the experimental group with SD or to the control group without SD. There were no differences between the two groups regarding their clinical characteristics (Table 1). The study was carried out during 3 consecutive weeks. Treatment (six nights of total SD in the experimental group and

TABLE 1. Patients' Characteristics

Variable	Whole Sample	Sleep Deprivation Group	Control Group	Statistical Comparison
No. patients (N)	19	9	10	
Age				
M	37.2	37.0	37.4	$t = -0.107; df = 17; p = .92$
SEM	1.8	2.7	2.6	
Gender				
Male (N)	11	4	7	$\chi^2 = 1.269; df = 1; p = .37$
Female (N)	8	5	3	
Type of MDD				
Single episode (N)	14	7	7	$\chi^2 = 0.148; df = 1; p = 1.00$
Recurrent episode (N)	5	2	3	
Severity of depression at baseline as assessed by				
Hamilton Depression Rating Scale				
M	26.0	26.2	25.8	$t = 0.218; df = 17; p = .83$
SEM	0.9	1.9	0.8	
Beck Depression Inventory				
M	30.3	28.8	31.6	$t = -0.882; df = 17; p = .39$
SEM	1.6	1.7	2.6	

SEM = standard error of the mean.

Treatment



Assessments

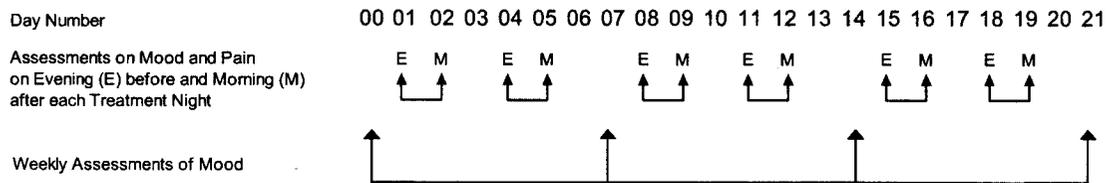


Figure 1. Experimental design and time schedule.

undisturbed night sleep in the control group) and measurements were conducted as follows: evening testing session regarding mood and pain measurements (7:00 PM) on day 1 with subsequent first treatment night and a morning testing session (8:00 AM) on day 2. This evening-morning sequence of measurements was chosen to avoid the effect of depressiogenic daytime naps after SD on our outcome variables. On day 4 to day 5, each patient underwent the same experimental condition, as just described. This sequence of treatments and measurements was repeated during the second (i.e., third and fourth treatment night from day 8 to 9 and 11 to 12, respectively) and third (i.e., fifth and sixth treatment night from day 15 to 16 and 18 to 19, respectively) treatment week (Figure 1). Accordingly, treatment nights were separated by intervals of 2 to 3 days with normal (recovery) night sleep.

Experimental Treatment Conditions

SD was performed according to a standard protocol. A staff member monitored the patient and ensured that the patient stayed awake from 8:00 PM to 7:00 AM and was engaged in standardized activities (including conversation, watching television, going for a walk, or playing games). The subject's behavior was recorded each hour. The patient received breakfast before the morning testing session at 8:00 AM.

The protocol for the control group with undisturbed night sleep also started immediately after the evening testing at 8:00 PM. Lights were turned off between 10:00 PM and 11:00 PM to enable sleep. Each patient of the control group was awakened at 7:00 AM, and breakfast was served before the morning measurements (8:00 AM).

Pain and Mood Parameters

Two groups of parameters were assessed: those targeting pain (i.e., sensitivity to noxious and nonnoxious stimuli, spontaneous pain) and those targeting mood and well-being. Furthermore, the sleep quality of the control group was used as control variable.

Sensitivity to noxious and nonnoxious stimuli: cold detection threshold (CDT), warmth detection threshold (WDT), cold pain threshold (CPT), and heat pain threshold (HPT) were determined in this order by using the method of limits with ascending stimulus intensities. A Thermal Sensory Analyser (TSA-2001, Medoc Ltd.) was used. The contact thermode (stimulation surface of 3.2 × 3.2 cm²) was attached to the center of the volar

forearm. Beginning at a baseline temperature of 32.0°C, five stimuli were applied for each of the four thermal thresholds. To avoid tissue damage, the cutoff temperature was 52.0°C and 0°C, respectively. Subjects were instructed to press a button as soon as they felt a change in temperature (CDT and WDT) or the onset of pain sensation (CPT and HPT). To minimize artifacts due to reaction time, we used slow rates of temperature change (18). This rate was ±1°C/s for the two detection thresholds and ±1.5°C/s for the two pain thresholds. Each time subjects pressed the button, the temperature returned to the baseline temperature, which was held constant until the next trial. CDT, WDT, CPT, and HPT were computed by averaging the temperature readings of the five successive stimuli designed for each threshold (relative to baseline in the case of the thermal detection thresholds, absolute in the case of the thermal pain thresholds).

Current pain complaints (number of pain sites, their intensity, and unpleasantness) were assessed by a pain questionnaire, which was used in former studies on patients with depression (19). For the present study, the instruction of the questionnaire was slightly adapted to evaluate exclusively current pain complaints. On two schematic drawings of the front and rear body, the subjects were asked to mark each location in which they currently experienced pain. This allowed for counts of the number of painful sites. Afterward, subjects were asked to rate the intensity and unpleasantness of pain for each site at separate horizontal visual analogue scales of 100 mm. To assess overall pain intensity and pain unpleasantness, the visual analogue scale ratings of all sites were summed for each of the two pain dimensions.

To evaluate acute effects of SD on mood and well-being, the Depression Scale (D-S) (20) and the Scale of Well-Being (Bf-S) (21) were administered at each evening and morning session. Both inventories are particularly designed to assess short-term variations of mood states. The D-S is a 16-item self-rating scale to evaluate the severity of depressive symptoms (not including pain complaints). More general aspects of emotional well-being (e.g., fatigue) and positive mood states (e.g., extraversion) are tracked in the self-rating Bf-S. The higher the score on each scale, the worse the patient's condition is at the time of evaluation.

Long-term changes of depressive symptoms during the course of treatment were assessed by the Beck Depression Inventory (BDI) (22) and Hamilton Depression Rating Scale (HDRS) (23). A psychiatrist not involved in cognitive

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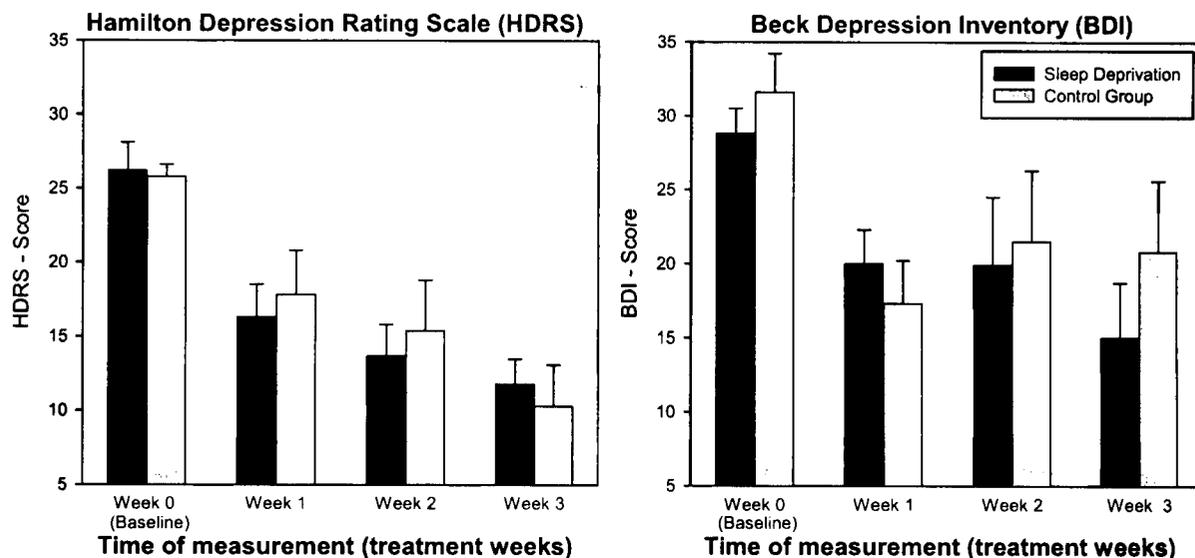


Figure 2. Weekly ratings of depression (mean \pm SEM) under the condition of cognitive behavioral treatment with or without sleep deprivation therapy.

behavioral treatment or in the evening and morning assessments performed HDRS. These scales were used at baseline and after each treatment week.

To control for sufficient night sleep in the control group, a sleep questionnaire was administered at the morning testing sessions to evaluate sleep quality during the preceding night. Although subjective measures of sleep quality are not as reliable as objective polysomnographic recordings, at least a few subjective sleep variables correspond with recorded objective sleep characteristics (24). The questionnaire used consists of questions concerning sleep duration, sleep latency and frequency as well as duration of awakenings (25). Furthermore, the questionnaire evaluates several subjective aspects of night sleep (calmness, depth, restfulness) by ratings on a bipolar 5-point Likert scale (e.g., depth of sleep: +2 = "very deep"; +1 = "deep"; 0 = "balanced"; -1 = "superficial"; -2 = "very superficial").

Statistical Analysis

Data were analyzed using SPSS, version 11.0 (SPSS Inc., Chicago, IL). Results are presented as mean and standard error of the mean. Changes in pain parameters and mood (D-S, Bf-S) between the groups and over time were analyzed with an analysis of variance (ANOVA) for repeated measurements with one between-subject factor ("treatment" = SD therapy) and two within-subject factors, which should evaluate "short-term" (from evening to morning of each treatment night) or "long-term" (over the 3 weeks of treatment) effects.

Weekly obtained parameters of mood and well-being (HDRS, BDI) were analyzed by an ANOVA with one between-subject factor ("treatment" = SD therapy) and one within-subject factor ("time"), which evaluate treatment and time-related changes from the baseline week over the following 3 weeks. In all analyses, the factor "treatment" refers to comparisons between SD and control nights.

In the case of Mauchly's test of sphericity being significant, adjusted degrees of freedom according Greenhouse-Geisser (GG) were used. Post hoc pair-wise comparisons were performed using *t*-tests for dependent samples to detect differences across time.

Additionally, correlation (Pearson) analyses for all patients were computed to determine how overnight changes of mood were related to those of pain. For this purpose, difference scores for each separate treatment night (morning scores— evening scores) were used. The significance level was set at $\alpha < 0.05$.

Data from the sleep questionnaire were analyzed descriptively.

RESULTS

Treatment Effects on Affective Symptoms

A marked improvement in the core symptoms of depression assessed weekly was observed from baseline week to the

final assessment after the third week of treatment (Figure 2). ANOVA revealed a significant main effect for "time" in HDRS ($F(3,51) = 29.647$; $p < .001$) and BDI (GG corrected $F(1.806,30.7) = 8.042$; $p = .002$), but no main effect for "treatment" (SD therapy) ($F(1,17) = 0.014$; $p = .91$ for HDRS and $F(1,17) = 0.204$; $p = .63$ for BDI, respectively). Post hoc analyses for HDRS by using pooled data from both groups showed a substantial decrease of depressive symptoms from week 0 (baseline) to the end of treatment week 1 ($t = 4.868$; $df = 18$; $p < .001$) and slighter but continuous reductions over the further course of treatment (week 1 versus week 2: $t = 2.267$; $df = 18$; $p = .04$; week 2 versus week 3: $t = 2.177$; $df = 18$; $p = .04$). A significant reduction of the BDI scores was only detected from baseline to the end of the first treatment week ($t = 4.817$; $df = 18$; $p < .001$) whereas the differences between the following measurements remained insignificant. Because there was no interaction between "treatment" and "time" (HDRS: $F(3,51) = 0.429$; $p = .73$; BDI: GG corrected $F(1.806,30.7) = 0.775$; $p = .46$), an additional long-term benefit of SD therapy was not found.

Based on the measurements of current mood and well-being during evening and morning sessions, a moderate but statistically nonsignificant effect of SD, as indicated by a close to significance ANOVA interaction between "treatment" (SD therapy) and the within-factor "short-term" ($F(1,17) = 4.293$; $p = .05$), was found for the D-S. As shown in Figure 3, patients who underwent SD developed an overnight amelioration of depressive mood in comparison to patients with undisturbed night sleep. Although overnight improvement of mood after SD was evident in each single night, *t* tests evaluating changes from evening to morning in the SD group showed a significant reduction of D-S scores only during the first treatment night (day 1 versus 2: $t = 2.363$; $df = 8$; $p = .046$). Compared with the SD group, the evening-morning differences in the control group were characterized by smaller

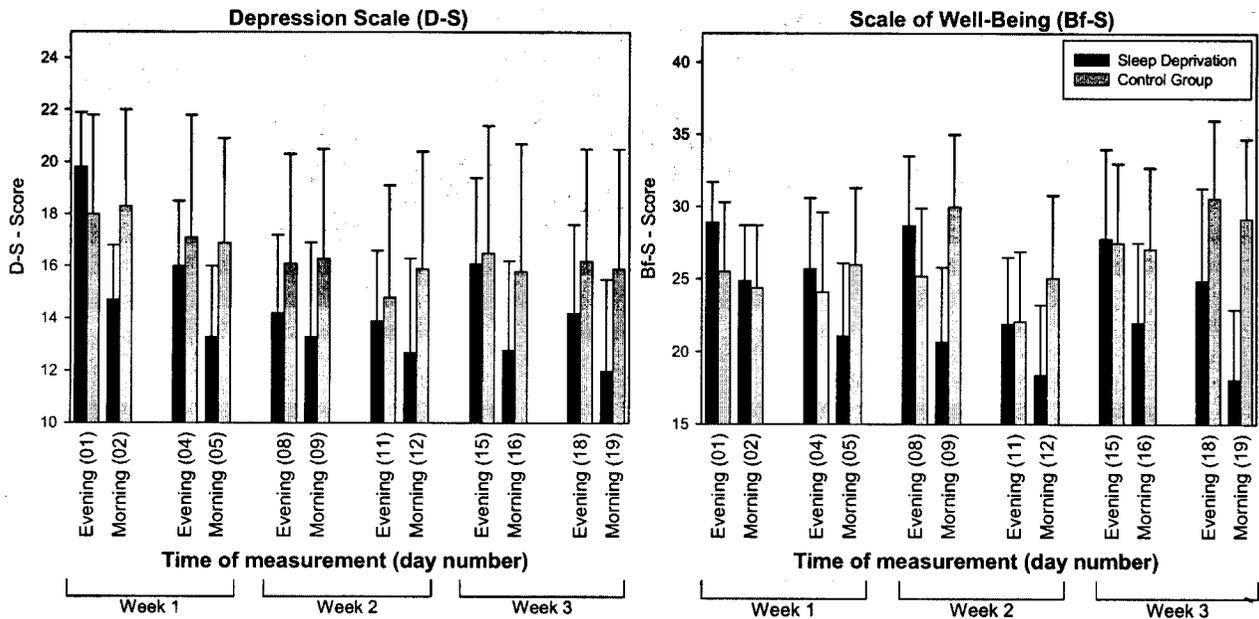


Figure 3. Self-ratings of mood and well-being (mean \pm SEM) on the evening before and the morning after sleep deprivation or control night.

changes or by changes in the opposite direction. The Bf-S ratings revealed a similar overnight pattern, although to a lesser extent. This was indicated by an insignificant ANOVA interaction between "treatment" and the within-factor "short-term" ($F(1,17) = 2.087; p = .17$).

In contrast to the findings based on the weekly assessments of depressive symptoms (HDRS and BDI), the main effect of time ("long-term") for the parameters of current mood was less evident. A statistically nonsignificant effect was noted for the D-S data (GG corrected $F(2,479,42.150) = 2.748; p = .06$), for which post hoc analyses using pooled data (for both groups as well as for the evening and morning sessions) revealed a significant reduction of depressive mood from day 1/2 to day 8/9 ($t = 2.123; df = 18; p = .048$), 11/12 ($t = 2.523; df = 18; p = .02$) and 18/19 ($t = 2.255; df = 18; p = .04$), respectively. No main effect "long-term" ($F(5,85) = 1.740; p = .13$) and therefore no such significant differences in post hoc analyses were found for the Bf-S.

Treatment Effects on Pain and Somatosensory Thresholds

As shown in Figure 4, SD decreased thermal pain thresholds from evening to the following morning during the course of six treatment nights, whereas a clearly different pattern was found under the condition of undisturbed night sleep.

For HPT, the two-way interaction between "treatment" and "short-term" was found to be highly significant ($F(1,17) = 11.072; p = .004$). The SD group showed an overnight decrease of HPT during each single treatment night. Post hoc analyses, comparing the evening and morning values, revealed a significant decrease of HPT in the course of the first night (day 1 versus 2: $t = 2.568; df = 8; p = .03$) but nonsignificant decreases during the further nights the second (day 4 versus 5: $t = 1.694; df = 8; p = .13$), third (day 8 versus 9: $t = 1.771; df = 8; p = .11$), fourth (day 11 versus 12: $t = 2.136; df = 8;$

$p = .07$), fifth (day 15 versus 16: $t = 0.657; df = 8; p = .53$) and sixth (day 18 versus 19: $t = 2.041; df = 8; p = .08$) SD night. In marked contrast to the experimental SD group, the control group presented an increase of HPT from evening to morning during almost all nights. However, post hoc analyses failed to confirm significant differences (all p values above .10). Further within-comparisons for the SD group suggested increases of HPT from the morning after SD to the evening values before the next SD (i.e., after recovery sleep), but these differences failed to reach statistical significance (day 2 versus 4: $t = -1.843; df = 8; p = .10$; day 5 versus 8: $t = -2.155; df = 8; p = .06$; day 12 versus 15: $t = -1.967; df = 8; p = .09$; day 16 versus 18: $t = -2.267; df = 8; p = .05$) with one exception (day 9 versus 11: $t = -2.949; df = 8; p = .02$). The regular return to the starting level emphasizes that the effect of SD on HPT was only short-term. Furthermore, a significant "long-term" effect (GG corrected $F(3,387,57.580) = 3.391; p = .008$) indicated a continuous and SD-independent increase of HPT in the course of the 3 weeks of treatment. Pair-wise comparisons with pooled data revealed that HPT in the third week of treatment were—with a small exception—significantly higher than during the initial stages of treatment (day 1/2 versus day 15/16: $t = -2.080; df = 18; p = .05$; day 1/2 versus day 18/19: $t = -2.130; df = 18; p = .047$; day 4/5 versus day 15/16: $t = -4.327; df = 18; p < .001$; day 4/5 versus day 18/19: $t = -2.557; df = 18; p = .02$).

The statistical analysis of CPT produced a similar pattern of results although it was limited by the fact that only some of the patients ($n = 11$) consistently developed a sensation of cold pain above the lower temperature cutoff at 0°C. Missing data did not stem systematically from specific treatment conditions (five patients in SD group versus four patients in control group) or times of measurement. SD produced an overnight decrease of CPT whereas a change in the opposite

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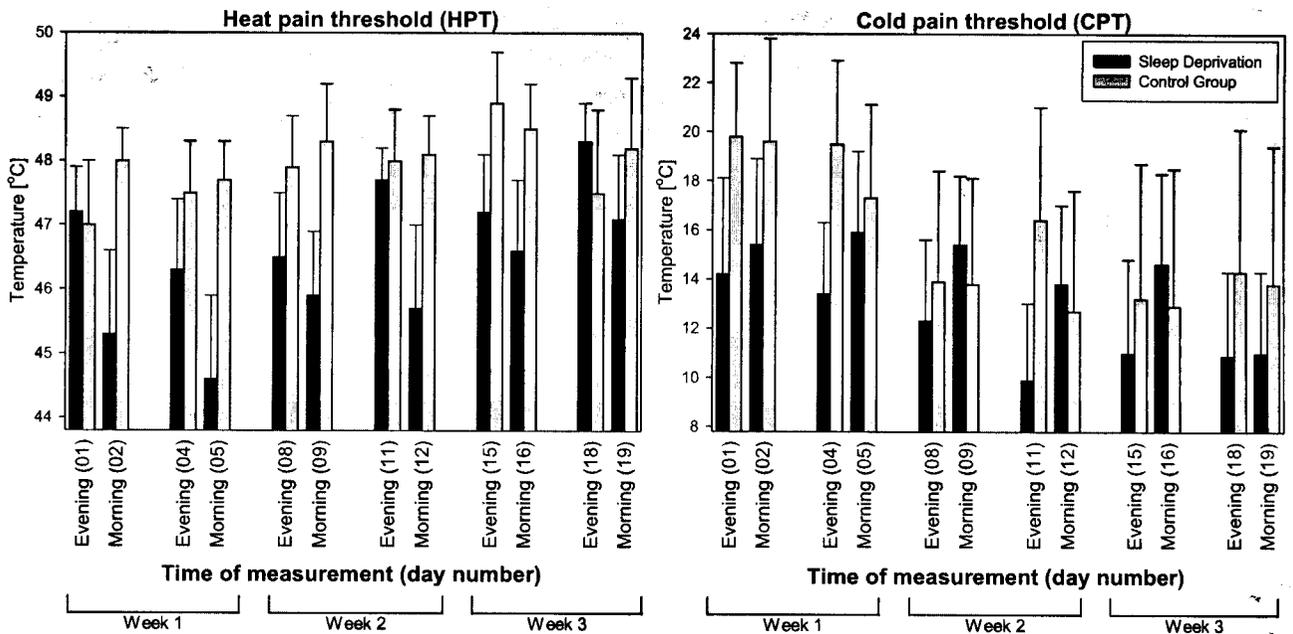


Figure 4. Thermal pain thresholds (mean \pm SEM) on the evening before and the morning after sleep deprivation or control night. Bars represent the absolute threshold temperature, i.e., decreased heat pain threshold are indicated by lowered temperature values, whereas decreasing cold pain thresholds are expressed in elevated temperature values.

direction was apparent under the condition of undisturbed night sleep (Figure 4). However, an interaction between "treatment" and within-factor "short-term" remained insignificant ($F(1,9) = 4.402$; $p = .07$). After recovery nights, CPT returned to pretreatment levels in the SD group as indicated by consistent but statistically insignificant changes. Interestingly, the "long-term" effect on CPT was similar to that of HPT. As shown in Figure 4, both treatment groups developed a continuous but statistically nonsignificant increase of CPT during the study period ("long-term": GG corrected $F(2.395,21.559) = 2.815$; $p = .07$). The most obvious changes were detected between the first and the last treatment nights (t tests with pooled data comparing day 1/2 versus day 15/16, day 1/2 versus day 18/19, day 4/5 versus day 15/16 and day 4/5 versus day 18/19), but failed to reach statistical significance.

Although the data on thermal pain thresholds indicate a substantial overnight decrease caused by SD, such an effect was not observed for detection thresholds for warmth and cold (Figure 5). The interaction effect between "treatment" and within-factor "short-term" remained clearly nonsignificant for the CDT ($F(1,17) = 0.178$; $p = .68$) and WDT ($F(1,17) = 0.598$; $p = .45$). Furthermore, CDT and WDT remained nearly unchanged over the six treatment nights ("long-term": GG corrected $F(2.196,37.324) = 1.198$; $p = .32$ and $F(5,85) = 0.738$; $p = .60$, respectively).

Treatment Effects on Pain Complaints

As shown in Figure 6, SD increased the number of pain sites and the ratings of unpleasantness after nearly every night. These overnight changes were statistically expressed in a significant ANOVA interaction between "treatment" and within-

factor "short-term" (number of painful sites: ($F(1,17) = 5.424$; $p = .03$, rating of unpleasantness: ($F(1,17) = 6.253$; $p = .02$)). In a similar manner as described for HPT and CPT, the increased number of pain sites as well as the more pronounced ratings of unpleasantness after SD were transient and annulled by recovery sleep. All "short-term" effects described were only significant in the overall analyses by ANOVA but failed significance in the post hoc analyses for single effects. A similar pattern of results was obtained by ANOVA for the ratings of pain intensity but failed to reach statistical significance for the interaction between "treatment" and "short-term" effects ($F(1,17) = 4.029$; $p = .06$). Apart from these "short-term" effects of SD, no "long-term" time effects on the subjective pain ratings were detected (number of painful sites: GG corrected $F(3.268,55.563) = 0.915$; $p = .45$, rating pain intensity: GG corrected $F(2.536,43.117) = 1.660$; $p = .20$; rating of pain unpleasantness: GG corrected $F(2.308,39.230) = 1.696$; $p = .19$).

Correlation Analysis Between Overnight Changes of Mood and Pain

The correlation coefficients between the changes (evening-morning differences) of mood (D-S, Bf-S) and HPT were weak (ranging between -0.171 and 0.400) and insignificant (all $p > .05$). There were also insignificant correlations between the overnight changes of mood and CPT (ranging between -0.410 and 0.481 ; all $p > .05$), except for substantial and significant negative correlations between changes of mood and CPT in the course of the third ($r = -0.612$ for D-S, $r = -0.585$ for Bf-S; each with $p < .05$) and the fifth treatment night ($r = -0.632$ for D-S, $r = -0.782$ for Bf-S; each with $p < .05$). Strong statistically significant correlations between overnight changes of mood and subjective measures

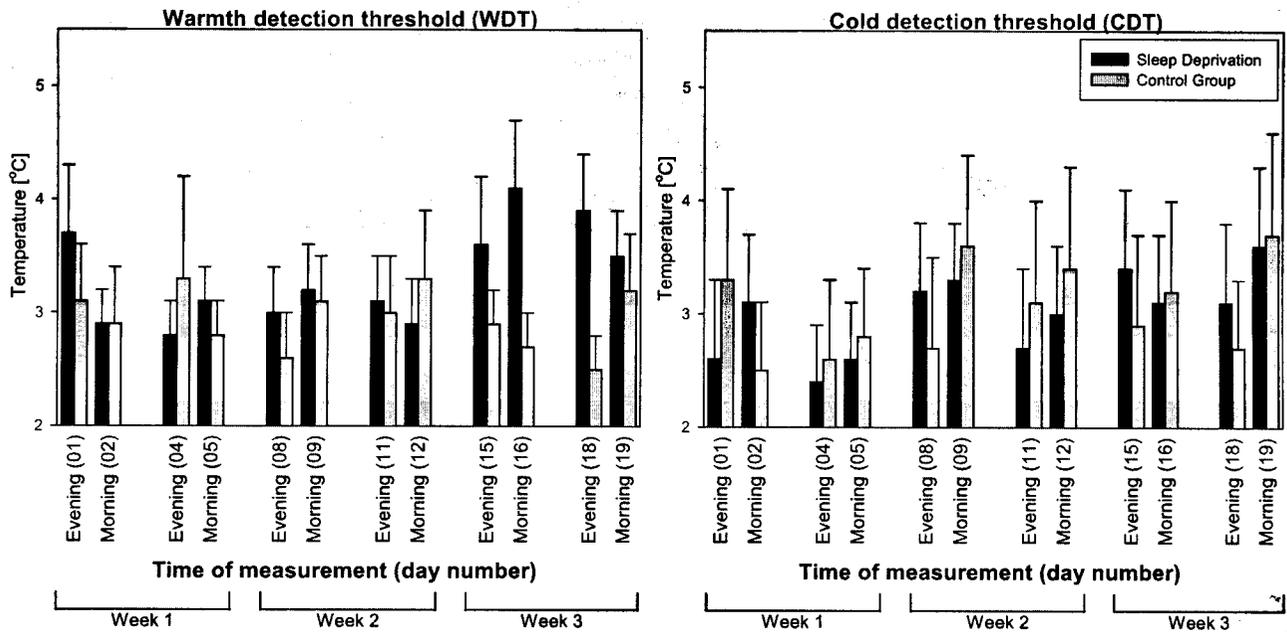


Figure 5. Thermal detection thresholds (mean ± SEM) on the evening before and the morning after sleep deprivation or control night.

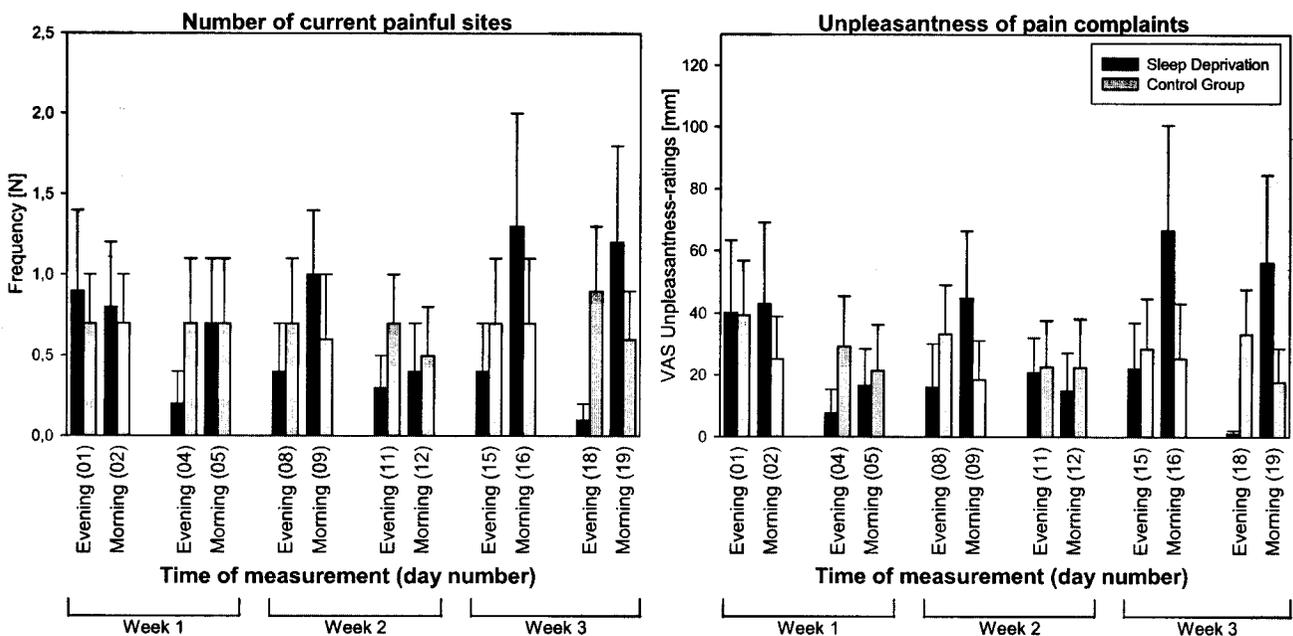


Figure 6. Pain complaints (mean ± SEM) on the evening before and the morning after sleep deprivation or control night.

of pain (number of sites, unpleasantness, intensity), ranging from 0.405 to 0.799 ($p < .1$ and $p < .001$, respectively), were only obtained for the fourth treatment night, indicating that mood improvement just during this night was associated with an alleviation of pain complaints.

Subjective Sleep Quality of Control Group

The subjective ratings of sleep quality revealed that patients of the control group experienced sufficient night sleep during the six nights. Mean sleep duration of the six control nights ranged from

7.4 to 6.7 hours, whereas the averaged sleep latency ranged between 34.3 and 74.5 minutes. The mean frequency of awakenings was minimal 0.8 and maximal 2.1 per night with a duration of awakenings during nighttime ranging from 27.5 to 56.5 minutes. The results of the Likert scale ratings (calmness, depth, and restfulness of sleep) showed that at most six patients per night expressed estimations below the neutral category, indicating a trend toward reduced sleep quality. Descriptively, a change of the subjective sleep characteristics in the course of the treatment period was not observed.

DISCUSSION

SD therapy is well known for its fast but transient effects on core symptoms of depression. Thus, it is an ideal tool to study the intraindividual linkage between mood and pain during short-term periods of improvement of depressive symptoms.

Compared with the control group with undisturbed sleep, our sleep-deprived patients experienced a moderate but statistically nonsignificant overnight improvement of mood, which was transient and annulled by recovery sleep. The fact that this effect of SD failed to reach statistical significance is probably due to a small sample size (i.e., low statistical power), which represents a limitation of our study. Because our study was primarily designed to evaluate short-term effects of SD by assessing evening-morning changes, data regarding the later daytime course of mood (e.g., on evening after treatment night) cannot be provided. Therefore, it cannot be excluded that a more robust mood response—possibly in a subgroup of patients—occurred later in the day.

All patients similarly showed a significant decline of depressive symptoms as evidenced by the weekly assessments over the 3 weeks of cognitive-behavioral therapy, although a mild to moderate severity of depressive symptoms was still present after treatment. SD did not add substantially to the long-term alleviation of depressive symptoms in the course of cognitive-behavioral therapy. This finding is not surprising given the high rates of relapses occurring after recovery sleep, which is in accordance with the literature (15). Although a few studies suggest a sustained antidepressive response after monotherapy with repeated SD (e.g., (26)), only combination treatments such as with lithium or light therapy have been clearly shown to attenuate relapses after recovery sleep after SD (15). In summary, we observed moderate but nonsignificant short-term and substantial long-term variations in the intensity of affective symptoms, which was a prerequisite for our investigation of covariation with pain parameters.

Because the primary aim of the study was to examine the short-term effects of SD on affective symptoms and pain in depression, the issue of how the overnight improvement of mood was accompanied by changes in the pain parameters is discussed first. SD produced a reduction of pain thresholds and an increase in clinical pain complaints. A significant effect of SD was observed on HPTs (i.e., decreasing HPT) but a similar overnight change pattern was also found for CPTs (i.e., decreasing CPT). Due to missing data, leading to a further reduction of statistical power, CPT findings presumably failed to reach statistical significance; another reason may be the lower reliability of this parameter (27).

With regard to the impact of short-term clinical improvement of depression on pain sensitivity, our findings cannot be compared with other studies because no study has yet investigated such effects. It remains speculative whether the induced enhanced pain sensitivity indicates a transient normalization from a decreased responsiveness to noxious stimuli. Because our experimental design did not include a nonclinical control

group, we do not know whether the pain thresholds of our patients would have differed before or after SD from those of healthy individuals. However, the assumption of an initially decreased heat pain sensitivity in our sample is well-supported by a number of studies in depressive patients which reveal a hypoalgesic response to noxious thermal stimuli similar to those applied in the present study (4).

One might conclude that the observed overnight effects on pain sensitivity are tightly linked to the amelioration of symptoms of depression produced by SD. The idea of a linkage between short-term changes of mood and pain sensitivity in depression is also supported by the finding that recovery sleep induced simultaneously a relapse of mood toward depression and a change of pain sensitivity toward the starting level before SD. On the other hand, our data also provide evidence that the overnight change of mood was not strongly related to changes of pain sensitivity, as indicated by mainly weak correlations between short-term changes of mood and pain sensitivity. Furthermore, studies performed on healthy subjects revealed that SD also produces short-term hyperalgesic effects (for a review, see (28)), which vanished after recovery sleep (29,30) although no change or even a deterioration of mood after SD were reported (31). Based on these findings of hyperalgesic changes induced by SD, which were obtained in responses to phasic and tonic pain stimuli, one might conclude that this effect does not depend either on the initial psychopathology or on the mood change after SD.

In contrast to the measures of thermal pain thresholds, SD did not affect WDT and CDT. This observation emphasizes that the enhanced responsiveness after SD was specific for noxious stimuli, which agrees with our previous study on healthy subjects (30).

The short-term effects of SD on pain complaints consisted of a significantly increased frequency of pain sites as well as enhanced ratings of unpleasantness of pain complaints, whereas increased ratings of pain intensity failed to reach statistical significance. The overnight increase of pain complaints under SD was transient and vanished after recovery sleep, a temporal pattern, which was similarly observed for the measures of pain sensitivity. Accordingly, the patients experienced themselves as more affected by pain just in a phase of mood improvement. When comparing these results with SD studies in healthy subjects, it is of interest to note that an augmentation of pain complaints was first observed after three consecutive nights of selective SD (32,33). Therefore, one can assume that patients with depression are especially vulnerable to SD in respect to the mediation of clinical pain. This implicates that a transient development or augmentation of pain is—like daytime sleepiness or hypomanic episodes—a potential adverse side effect of SD therapy, but this finding should be viewed as preliminary which requires further confirmation.

How can the increase in clinical pain be explained? An explanation might be that the transiently enhanced pain sensitivity contributes to the augmentation of clinical pain. However, the cross-sectional weak correlations between clinical

pain measures and pain thresholds in patients with depression (19) do not support this explanation.

Our findings are further evidence for a differential effect of antidepressant therapy on core symptoms of depression and pain. Regarding short-term effects, the overnight changes of mood were not consistently correlated with those of pain sensitivity and pain complaints. Concerning long-term changes, affective symptoms of depression markedly diminished whereas pain thresholds showed a gradual and significant increase toward the end of the study period; the various measures of pain complaints, however, remained nearly unchanged. As to the successive decrease of heat pain sensitivity during the 3-week treatment period, it is likely that this observation reflects an adaptation to noxious thermal stimuli due to the frequently conducted threshold assessments but no change in pathophysiology of depression. Nevertheless, this pattern of findings suggests that an improvement of mood in the course of cognitive-behavioral therapy was definitely not accompanied by a similar amelioration of pain processing, i.e., a normalization of pain thresholds from increased starting levels and a decline of clinical pain. The affective and pain symptoms of depression seem to follow different short-term and long-term courses. Thus, our study provides further evidence that effects of antidepressant treatment on mood have to be differentiated from their analgesic actions. The latter apparently holds true for both, patients with depression and patients with chronic painful conditions (34).

With regard to the underlying mechanisms, SD is assumed to exert its antidepressive effect among others via an enhanced serotonergic neurotransmission (35). In view of numerous experimental and clinical reports, highlighting the role of serotonin for antinociceptive actions, our finding of increased pain after SD seems contradictory to this idea. On the other hand, several studies suggest that serotonin is not only involved in pain inhibitory mechanisms, but also in pronociceptive actions depending on the receptor subtype it acts on (for a review, see (36)). Thus, the underlying neurobiologic mechanisms, by which SD produces differential effects on mood and pain, remain unclear and could not be clarified by the present design. Hence, further studies are necessary to investigate the longitudinal relationship of pain sensitivity, clinical pain complaints, and mood under treatments with definite specificity for certain neurobiologic mechanisms of action.

REFERENCES

1. Von Korff M, Simon G. The relationship between pain and depression. *Br J Psychiatry Suppl* 1996;30:101-8.
2. Von Knorring L, Perris C, Eisemann M, Eriksson U, Perris H. Pain as a symptom in depressive disorders. I. Relationship to diagnostic subgroup and depressive symptomatology. *Pain* 1983;15:19-26.
3. Karp JF, Scott J, Houck P, Reynolds CF III, Kupfer DJ, Frank E. Pain predicts longer time to remission during treatment of recurrent depression. *J Clin Psychiatry* 2005;66:591-7.
4. Dickens C, McGowan L, Dale S. Impact of depression on experimental pain perception: a systematic review of the literature with meta-analysis. *Psychosom Med* 2003;65:369-75.
5. Bär KJ, Brehm S, Boettger MK, Boettger S, Wagner G, Sauer H. Pain perception in major depression depends on pain modality. *Pain* 2005;117:97-103.
6. Lautenbacher S, Krieg JC. Pain perception in psychiatric disorders: a review of the literature. *J Psychiatr Res* 1994;28:109-122.
7. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
8. Lautenbacher S, Roscher S, Strian D, Fassbender K, Krumrey K, Krieg JC. Pain perception in depression: relationships to symptomatology and naloxone-sensitive mechanisms. *Psychosom Med* 1994;56:345-52.
9. Von Knorring L. An intraindividual comparison of pain measures, averaged evoked responses and clinical ratings during depression and recovery. *Acta Psychiatr Scand Suppl* 1974;255:109-20.
10. Schreiber S, Shmueli D, Grunhaus L, Dolberg OT, Feldinger E, Magora F, Shapira SC. The influence of electroconvulsive therapy on pain threshold and pain tolerance in major depression patients before, during and after treatment. *Eur J Pain* 2003;7:419-24.
11. Gormsen L, Ribe AR, Raun P, Rosenberg R, Videbech P, Vestergaard P, Bach FW, Jensen TS. Pain thresholds during and after treatment of severe depression with electroconvulsive therapy. *Eur J Pain* 2004;8:487-93.
12. Bär KJ, Greiner W, Letsch A, Kobele R, Sauer H. Influence of gender and hemispheric lateralization on heat pain perception in major depression. *J Psychiatr Res* 2003;37:345-53.
13. Barbini B, Benedetti F, Colombo C, Guglielmo E, Campori E, Smeraldi E. Perceived mood and skin body temperature rhythm in depression. *Eur Arch Psychiatry Clin Neurosci* 1998;248:157-60.
14. Benedetti F, Barbini B, Colombo C, Campori E, Smeraldi E. Infradian mood fluctuations during a major depressive episode. *J Affect Disord* 1996;41:81-7.
15. Giedke H, Schwarzler F. Therapeutic use of sleep deprivation in depression. *Sleep Med Rev* 2002;6:361-77.
16. Wittchen HU, Zaudig M, Fydrich T. *Strukturiertes Klinisches Interview für DSM-IV Achse I und II (SKID-I und SKID-II)*. Göttingen: Hogrefe; 1997.
17. Hautzinger M, Stark W, Treiber R. *Kognitive Verhaltenstherapie bei Depressionen: Behandlungsanleitungen und Materialien*. 5th ed. Weinheim: Beltz PVU; 2000.
18. Yarnitsky D. Quantitative sensory testing. *Muscle Nerve* 1997;20:198-204.
19. Lautenbacher S, Sernal J, Schreiber W, Krieg JC. Relationship between clinical pain complaints and pain sensitivity in patients with depression and panic disorder. *Psychosom Med* 1999;61:822-7.
20. Zerssen D. *Die Depressionsskala*. Weinheim: Beltz; 1976.
21. Zerssen D. *Die Befindlichkeitsskala*. Weinheim: Beltz; 1976.
22. Hautzinger M, Bailer M, Worall H, Keller F. *Beck-Depressions-Inventar (BDI)*. Bern: Huber; 1995.
23. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatr* 1960;23:56-62.
24. Buysse DJ, Hall M, Tu XM, Land S, Houck PR, Cherry CR, Kupfer DJ, Frank E. Latent structure of EEG sleep variables in depressed and control subjects: descriptions and clinical correlates. *Psychiatry Res* 1998;79:105-22.
25. Hemmter U, Seifritz E, Hautzinger M, Müller MJ, Holsboer-Trachsler E. Serial partial sleep deprivation as adjuvant treatment of depressive insomnia. *Prog Neuropsychopharmacol Biol Psychiatry* 1995;19:593-602.
26. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res* 2000;95:43-53.
27. Park R, Wallace MS, Schulteis G. Relative sensitivity to alfentanil and reliability of current perception threshold vs von Frey tactile stimulation and thermal sensory testing. *J Peripher Nerv Syst* 2001;6:232-40.
28. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev* 2006;10:357-69.
29. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 2001;10:35-42.

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30. Kundermann B, Sernal J, Huber MT, Krieg JC, Lautenbacher S. Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med* 2004;66:932-7.
31. Heiser P, Dickhaus B, Opper C, Hemmeter U, Remschmidt H, Wesemann W, Krieg JC, Schreiber W. Alterations of host defence system after sleep deprivation are followed by impaired mood and psychosocial functioning. *World J Biol Psychiatry* 2001;2:89-94.
32. Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med* 1975;37:341-51.
33. Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. *J Rheumatol* 1999;26:1586-92.
34. Burt VK, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin JG, Stewart DE. Duloxetine for the treatment of major depressive disorder in women ages 40 to 55 years. *Psychosomatics* 2005;46:345-54.
35. Adrien J. Neurobiological bases for the relation between sleep and depression. *Sleep Med Rev* 2002;6:341-51.
36. Millan MJ. Descending control of pain. *Prog Neurobiol* 2002;66:355-474.