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Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers

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ABSTRACT

The experiment investigated the impact of sleep restriction on pain perception and related evoked potential correlates (laser-evoked potentials, LEPs). Ten healthy subjects with good sleep quality were investigated in the morning twice, once after habitual sleep and once after partial sleep restriction. Additionally, we studied the impact of attentional focussing on pain and LEPs by directing attention to (intensity discrimination) or away from the stimulus (mental arithmetic). Laser stimuli directed to the hand dorsum were rated as 30% more painful after sleep restriction (49 ± 7 mm) than after a night of habitual sleep (38 ± 7 mm). A significant interaction between attentional focus and sleep condition suggested that attentional focusing was less distinctive under sleep restriction. Intensity discrimination was preserved. In contrast, the amplitude of the early parasylvian N1 of LEPs was significantly smaller after a night of partial sleep restriction (−36%, $p < 0.05$). Likewise, the amplitude of the vertex N2–P2 was significantly reduced (−34%, $p < 0.01$); also attentional modulation of the N2–P2 was reduced. Thus, objective (LEPs) and subjective (pain ratings) parameters of nociceptive processing were differentially modulated by partial sleep restriction. We propose, that sleep reduction leads to an impairment of activation in the ascending pathway (leading to reduced LEPs). In contradistinction, pain perception was boosted, which we attribute to lack of pain control distinct from classical descending inhibition, and thus not affecting the projection pathway. Sleep-restricted subjects exhibit reduced attentional modulation of pain stimuli and may thus have difficulties to readily attend to or disengage from pain.

1. Introduction

Sleep restriction is commonly associated with alterations in pain perception. A recent large-scale epidemiological study of a representative sample of the general population in the United States – although based on very crude measures of pain and sleep – provided evidence that the duration of sleep had a strong impact on next day pain perception [16]. However, there is a conspicuous lack of experimental and clinical studies that substantiate this assumption. Recent psychophysiological studies gave evidence that the relationship between sleep and pain can be seen as reciprocal (reviewed in [35]). It is well-known that pain may disturb sleep, and sleep disturbances are thus often seen in patients suffering from chronic pain diseases [62]. Sleep restriction on the other hand, leads to hyperalgesia-like changes of pain perception on the following morning [54]. Additionally, disturbances of sleep continuity impair endogenous pain-inhibitory function [62], decrease pain thresholds and augment spontaneous pain [34,39,62].

Restricting sleep below an individual's optimum of sleeping hours can negatively affect psychological components like attention, cognitive throughput and mood on the day following a night of sleep restriction [18,25,59,71]. Pain perception can be substantially altered bi-directionally by variations in attentional focus, and painful stimuli are perceived as less intense when subjects are distracted and as more painful when they are focused on it [56]. Similar changes of cortical activation occur in brain areas associated with pain perception such as anterior cingulate cortex (ACC), insular cortex, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and thalamus [28,32,56].

Our current understanding is that pain is an integrated experience that encompasses a sensory–discriminative component and an emotional–motivational component associated with activation

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of the lateral and medial pain system, respectively [1,11]. Processing of the emotional subcomponent of pain perception is different from the sensory–discriminative subcomponent [10,49–52,60]. Our experimental investigation focuses on the sensory–discriminative component of pain. Hypotheses tested were first, whether sleep restriction alters perception of experimentally-induced pain, second, such altered pain perception is accompanied by altered cortical activation in the parasylvian cortex (insula/secondary sensory cortex; estimated by the N1 component of laser-evoked potentials), and/or cingulate cortex (estimated by the N2–P2 component of laser-evoked potentials), and third, whether sleep restriction alters attentional modulation of pain and nociceptive processing.

2. Methods

2.1. Subjects

Ten healthy subjects (8 male, 2 female, aged 21–44 years, mean: 25.3 ± 2.2) participated in the study. All subjects had a good sleep quality assessed by the Pittsburgh Sleep Quality Questionnaire Index (PSQI), which is a well validated and widely used 19-item measure of sleep quality [6,19,75]. An index of $\leqslant 5$ was required to include subjects ("good sleepers"). All subjects were recruited from research staff and medical students of the University of Mainz (Germany) and all gave their written consent. The study complied with the Declaration of Helsinki and the Local Ethics Committee approved the experimental procedure.

2.2. Sleep sessions

All subjects were investigated twice, once following a night of habitual sleep and once after a night of partial sleep restriction. Under habitual sleep subjects followed their normal sleep habits. Under the condition of partial sleep restriction subjects were instructed to sleep for not more than 4 h by staying awake during the first half of the night and to get up at about 7 am. Motor activity was monitored by Actiwatch actigraphs worn on the non-dominant wrist for both experimental nights (Cambridge Neurotechnology Ltd., Cambridgeshire, UK). Actigraphs are equipped with sensitive accelerometers and record subjects' level of activity by recording arm movement. Periods of low motor activity are present during sleep and thus this method is an indirect measure of sleep duration. Although indirect, actigraphy is a valid and widely accepted measure of wakefulness [13,25,55]. Sleep duration for the night when subjects followed their normal sleep habits averaged 7.20 ± 0.38 h. During the restricted sleep condition subjects stayed awake until the early morning equivalent to a sleep restriction of 3.33 ± 0.33 h. Accordingly, under sleep restriction average sleep duration was significantly shortened to 54% of habitual sleep (3.87 ± 0.28 h, $p < 0.001$). Given that short naps may escape the actigraph method the estimate of sleep restriction may have been moderately overestimated. Sleep sessions were separated by approximately one week (7 ± 1 day) and the order of sessions was balanced across volunteers.

2.3. Stimulation

Radiant heat stimuli eliciting moderately painful sensations ("pricking pain") were generated by an energy-controlled infrared thulium laser (StimuLaser, InPro, Norderstedt, Germany: 2.01 mm wavelength, 5 mm beam diameter, 3 ms stimulus duration at two different intensities of 410 and 520 mJ, 50% probability randomized [64]). Laser pulses were transmitted through an optic fibre and directed to the dorsum of the left and right hand. A visible light He–Ne pilot laser was used to identify the area to be stimulated. Subjects wore protective goggles throughout the experiment. To avoid nociceptor fatigue or sensitization by repeated stimuli [24] the laser beam was slightly moved to an area of naïve skin after each stimulus.

2.4. Modulation of the attentional focus

Trials were performed under three different attentional conditions. One third of the trials were conducted without any further specific instructions (neutral condition). In all other trials attention status during the painful stimulation was systematically varied, and volunteers were either challenged by focussing on the painful stimulus (discrimination between two different stimulus intensities, 410 and 520 mJ; attentional focussing) or directing attention away from the painful stimulus by a mental arithmetic task – serial subtraction of a two-digit number, e.g. 13 or 17 from a four-digit number, e.g. 6843 (distraction). The two different stimulus intensities were chosen to yield about 70% correct responses in a two-alternative forced-choice discrimination task [56]. Likewise, mental arithmetic tasks were performed under speed conditions (as many correct calculations as possible) that yielded a similar rate of correct responses. The accuracies of performance for the arithmetic and discrimination tasks were determined as follows: arithmetic performance (performance index) was calculated from the number of subtractions during the time period needed to run 20 laser stimuli (approximately 3 min) and the average fraction of correct results across runs according to the following formula: number of calculated steps $*$ (1 − error rate). For the pain intensity discrimination task we determined the percentage of correct responses (100 $*$ number of correct answers/total number of responses).

2.5. Experimental protocol

All experiments were conducted in the morning. Subjects woke up either spontaneously or assisted by alarm clocks at 7.00–7.30 h, got prepared for the day and had a light breakfast. They arrived at the laboratory at approximately 8.30 h am. First, actigraphs were collected and read out to control for adequate sleep behavior according to the instruction for that night. Then, the technical assistant prepared the subject for EEG/EP-recording, followed by artefact control (eye movements, masticatory muscle activity, etc.). Laser detection and pain threshold were assessed at around 9.30 h and the core experiments commenced at approximately 10 h.

In all subjects we recorded brain potentials evoked by radiant heat (laser-evoked potentials, LEPs). On each experimental day we recorded 12 blocks of 20 stimuli each. For 3 blocks we stimulated the left hand, for another 3 blocks the right hand and we then repeated the stimulation in mirrored order whereupon stimulation sides were balanced (right–left–left–right or vice versa). Each block comprised one run of each of the three different attentional conditions (distraction, neutral, and focusing).

Noxious laser stimuli were applied to the skin of the dorsum of either the left or the right hand. The inter-stimulus interval was varied between 6 and 12 s. For all blocks two different intensities (410 and 520 mJ) were applied in a pseudo-randomized order. The order of sleep conditions, the order of commencing body side and the order of attentional conditions within each block were balanced across subjects. At the end of each block, subjects were asked to rate the perceived pain intensity across a block of stimuli on a horizontal visual analogue scale (VAS) ranging from 0 mm ('no pain') to 100 mm ('most intense pain imaginable'). The experimental procedure including all 12 blocks took approximately 60 min in total.

2.6. EEG data evaluation

EEG data were recorded using Ag–AgCl-electrodes (band-pass 0.16–500 Hz, sample rate 1000 Hz) from Fz, Cz, Pz (vs. linked ear-

lobes), T7 and T8 (vs. Fz, international 10–20-system). For artefact control, the electrooculogram (EOG) was measured from supra- and infraorbital electrodes. Electrode impedance was maintained below 5 kΩ by cleaning the skin with a glass fibre eraser.

EEG data were imported and all analyses carried out using BESA (Brain Electrical Source Analysis, Version 4.2.28; Megis, Germany). Continuous EEG data were band-pass filtered from 1 to 70 Hz for N2–P2 analysis. In order to preserve their amplitudes no additional filtering was used to analyze the N1 components. EEG epochs including the somatosensory stimuli were subsequently extracted using an analysis time window of 3 s (1500 ms pre-stimulus to 1500 ms post-stimulus). For each epoch, a baseline correction was performed using a pre-stimulus window (from −200 to 0 ms). Trials contaminated by eye blink artefacts were eliminated (<20% of trials per block).

LEP data were collapsed over repetitions, and waveforms were averaged separately for each sleep condition (normal sleep, sleep restriction) and each attentional focus (focused attention, neutral, and distraction) in each volunteer. We measured the peak latency and the baseline-to-peak amplitude of the early response (N1) at the temporal electrode contralateral to the stimulated side (T8/T7 against Fz), and peak latencies and peak-to-peak amplitudes of the negative and positive (N2–P2) vertex response (Cz against A1/A2). According to their orientation these recordings are suitable to pick up activities of source dipoles originating from the parasylvian or cingulate cortex [22]. Since there were no significant side differences LEP data for the left and right hand were pooled. Thus 6 latency and amplitude values for all EEG components (N1, N2–P2) were obtained for each subject (2 sleep conditions × 3 attentional states). When an LEP component could not be safely identified, which occasionally occurred only for the N1 component it was replaced by average noise level (−2 μV) to avoid biasing by missing values.

2.7. Statistical analysis

Data were first analyzed separately for every sleep condition by one-way analysis of variance (ANOVA) for the impact of attentional focus. For analysis across the different sleep states, a two-way analysis of variance (ANOVA, sleep condition * attentional task) was calculated with repeated measures on pain ratings, and LEP amplitudes (N1, N2–P2). LEP amplitudes varied substantially across subjects and were log-normally distributed. Thus all LEPs were transformed into decadic logarithms to achieve secondary normal distribution [41,65]. Comparison between sleep conditions (habitual sleep vs. sleep restriction) were assessed by paired Student's *t*-tests. All statistical analyses were calculated using SPSS 15.0 (SPSS Inc., Illinois, USA). All data are presented as mean ± standard error of the mean (SEM).

3. Results

3.1. Cognitive performance

Cognitive performance as derived from the mental arithmetic task was significantly impaired after sleep restriction. Subjects lacking sleep exhibited a reduced performance (performance index: 40 ± 10) compared to the results following habitual sleep (62 ± 11, $p < 0.01$), which is a 36% reduction of performance (Fig. 1).

3.2. Sensory discrimination

The ability to discriminate between two different intensities of painful laser stimuli was not impaired by lack of sleep, and no differences occurred between the two sleep conditions (59 ± 5% vs. 62 ± 6% of correct responses, n.s.; Fig. 1).

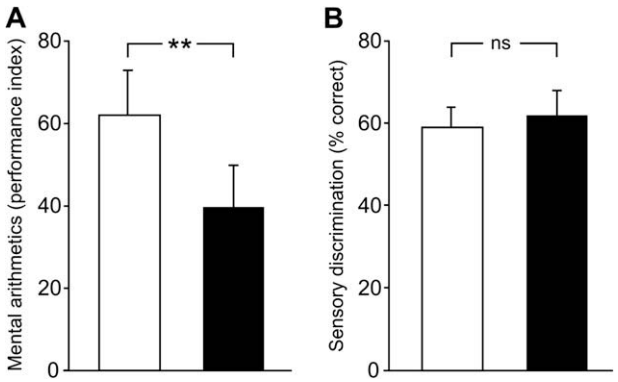

Fig. 1. Effects of sleep restriction on behavioral performances. (A) Mental arithmetic performance was significantly reduced following sleep restriction. (B) The accuracy of sensory discrimination was not impaired by restricted sleep. Open bars: normal sleep; filled bars: sleep restriction, $^{**}p < 0.01$.

3.3. Pain ratings

The perceived pain across all subjects and all attentional conditions was 38 ± 7 mm of VAS after a night of habitual sleep. Attentional modulation modified pain ratings significantly (ANOVA: $F_{2,18} = 5.83$, $p < 0.01$). Under attentional distraction VAS ratings were significantly lowered compared to focused or neutral conditions ($p < 0.01$, each; Fig. 2). Generally, subjects tended to perceive the laser stimuli as more painful after partial sleep restriction than after habitual sleep. Pain ratings across all attentional conditions were 49 ± 7 mm of VAS, equivalent to 30% increase compared to habitual sleep ($p = 0.07$). Pain ratings also tended to be modulated by the variation of the attentional focus, however attentional modulation was less prominent than after habitual sleep (ANOVA: $F_{2,18} = 1.70$, $p = 0.24$) suggesting that differences between attentional focuses are by far less distinctive under sleep restriction than after habitual sleep. Two-way ANOVA also revealed a significant interaction between attentional focusing and sleep condition (ANOVA: $F_{2,36} = 4.38$; $p < 0.05$), which was based on a more signif-

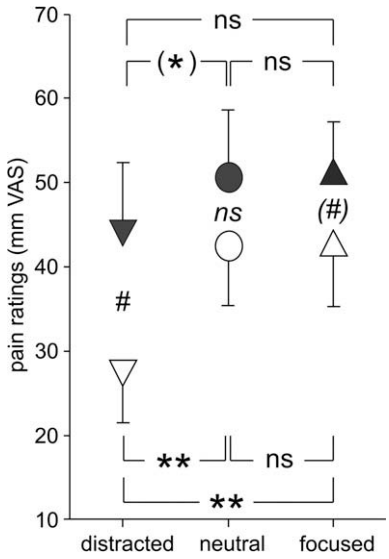

Fig. 2. Effects of sleep restriction on pain perception (VAS). Pain ratings tended to be higher and less modulated by attentional focusing. Open symbols: habitual sleep; filled symbols: sleep restriction. $^{(*)}p < 0.10$, $^{**}p < 0.01$ (for differences between attentional conditions) $^{(\#)}p < 0.10$, $^{\#}p < 0.05$ (for differences between sleep conditions).

icant pain rating difference during distraction (45 ± 8 vs. 28 ± 6 mm of VAS, $p < 0.05$). Post hoc *t*-tests revealed that the variation between normal and deprived sleep exhibited similar trends, but were lesser for focused attention ($p = 0.09$) or for the neutral condition ($p = 0.20$, Fig. 2).

3.4. Waveforms of LEPs

In all subjects, and under all attentional and sleep conditions, standard averaging analysis disclosed clear and reproducible LEPs time-locked to stimulus onset, following noxious laser stimulation. The earliest LEP component with latencies around 150 ms (N1: 145 ± 3 ms) was derived from the parasylvian cortex, followed by a large negative–positive LEP complex recorded from the vertex (N2–P2) with latencies at around 200 ms for the negativity (N2: 187 ± 6 ms) and 260 ms for the positivity (P2: 264 ± 5 ms). LEP latencies remained unchanged across the different sleep conditions (all $p > 0.30$; data not shown). Recordings of LEPs averaged across all attentional conditions in a typical subject are shown in Fig. 3 for both sleep conditions.

3.5. Early parasylvian N1 component of LEP

LEP amplitudes recorded from the parasylvian cortex and from the vertex were generally reduced after sleep restriction. After a night of habitual sleep, the amplitude of the early LEP component N1 averaged across all subjects and all attentional conditions was 5.4 μV ($\log_{10}$ mean: 0.734 ± 0.052). Attentional modulation of the N1 amplitude exhibited a trend that failed to be significant (ANOVA: $F_{2,18} = 2.37$, $p = 0.12$), however, under attentional distraction the N1 amplitude tended to be lowered compared to neutral or focusing conditions ($p = 0.07$ and $p = 0.08$, respectively; post hoc LSD test; Fig. 4A). After partial sleep reduction, the N1 component was reduced to 3.5 μV ($\log_{10}$ mean: 0.538 ± 0.036) equivalent to 36% decrease compared to habitual sleep (ANOVA sleep condition: $F_{2,18} = 5.37$, $p < 0.05$). Like pain ratings, attentional modulation of N1 LEP amplitude was strongly reduced under sleep restriction and did not reach statistical significance (ANOVA attentional condition: $F_{2,18} = 0.58$, $p = 0.57$), with no interaction between sleep and attentional conditions ($F_{2,36} = 1.06$, $p = 0.37$, Table 1).

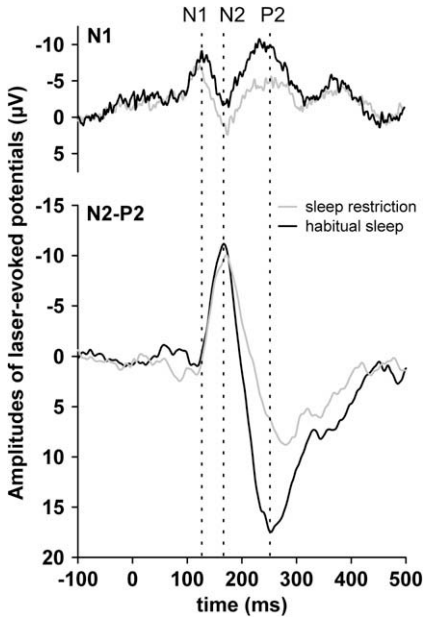

Fig. 3. Parasylvian responses (N1, upper panel) and vertex responses (N2–P2, lower panel) following normal and deprived sleep in a representative subject. LEP amplitudes were smaller after a night of restricted sleep than after normal sleep.

3.6. Vertex N2–P2 of LEP

A similar pattern was also found for the larger vertex N2–P2 component of the LEP. After a night of habitual sleep, the amplitude of the N2–P2 complex averaged across all subjects and all attentional conditions was 16.5 μV ($\log_{10}$ mean: 1.217 ± 0.076). Attentional modulation modified the N2–P2 amplitude significantly (ANOVA: $F_{2,18} = 9.63$, $p < 0.005$). Under attentional distraction the N2–P2 amplitude was significantly decreased compared to focused or neutral conditions ($p < 0.002$, each; Fig. 4B). After partial sleep reduction, the vertex N2–P2 was significantly reduced to 10.8 μV ($\log_{10}$ mean: 1.034 ± 0.078) equivalent to 34% decrease of amplitudes compared to habitual sleep (ANOVA: $F_{1,9} = 9.96$, $p < 0.02$). In contrast to normal sleep, attentional modulation of N2–P2 amplitude under sleep restriction was reduced although still significant (ANOVA attentional condition: $F_{2,18} = 6.00$, $p < 0.05$), with no interaction between sleep and attentional conditions ($F_{2,36} = 1.05$, $p = 0.37$, Table 1).

Generally, LEP amplitudes and pain ratings covary, when attention is modulated after habitual sleep, and – although to a lesser extent – also after sleep restriction. In contrast, when both sleep condition are compared this covariation is broken up, LEP amplitudes were substantially reduced, while pain rating rather increased. This segregated behavior of objective (LEP) and subjective dimension (pain rating) of nociceptive processing is depicted in Fig. 5.

4. Discussion

The present study revealed that after partial sleep restriction segregated changes in objective and subjective parameters occurred, pain-related evoked potentials (LEPs) were reduced whereas subjective pain perception rather increased. Additionally, following sleep restriction all parameters – pain ratings as well as N1 and N2–P2 amplitudes of the LEP – exhibited less attentional modulation. That leads to the assumption that a lack of sleep is associated with a significantly weaker ability to attend to, but also to disengage oneself from painful events. Cognitive performance of an mental arithmetic task involving working memory was significantly impaired after a night of partial sleep restriction whereas an equally demanding sensory discrimination task (pain intensity discrimination) not involving working memory was performed equally well after normal or restricted sleep.

4.1. Smaller laser-evoked potentials after sleep restriction point to reduced activity in the projection pathway

The amplitude of laser-evoked potentials (LEPs) was significantly diminished by approximately 1/3 following partial sleep restriction. Short term sleep restriction produces global decreases in brain activity, with larger reductions in stimulus-related activity in the cortico-thalamic network [66]. Wu et al. reported significant decreases in absolute cerebral glucose metabolic rate (CMRglu), a marker for neural activity, in the thalamus and cerebellum along with relative decreases of regional CMRglu in the thalamus, cerebellum and temporal cortex [76]. Sleep restriction resulted in decreased BOLD responses to serial subtraction among other areas in the ACC (anterior cingulate gyrus) and thalamus (pulvinar) [14]. A recent fMRI study has demonstrated a dose-dependent effect of sleep restriction resulting in exaggerated baseline activity of the thalamus, which is related to maintenance of wakefulness [67]. Moreover, exaggerated background activity resulted in a reci-

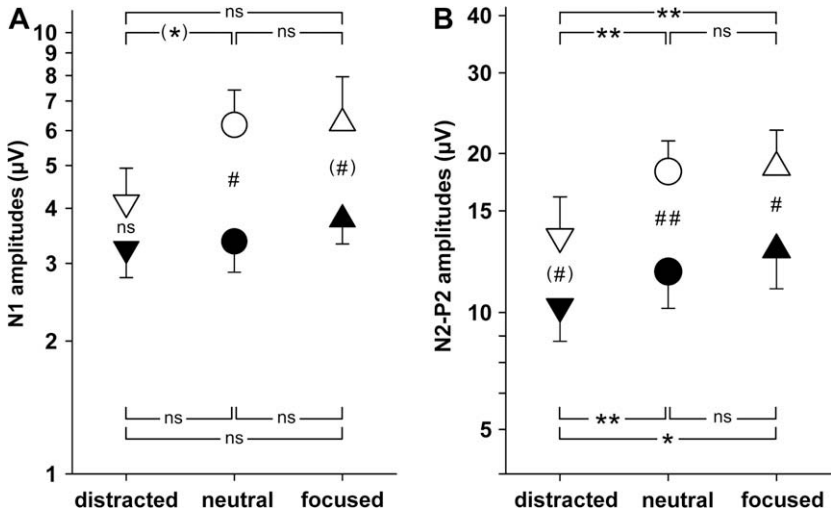

Fig. 4. Effects of sleep restriction on laser-evoked potentials. The amplitudes of the parasylvian N1 component of the LEP (A) and the vertex component of the LEP (B) were reduced and less modulated by attentional focusing. Open symbols: habitual sleep; filled symbols: sleep restriction. $^{(*)}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$ (for differences between attentional conditions) $^{(\#)}p < 0.10$, $^{\#}p < 0.05$, $^{\#\#}p < 0.05$ (for differences between sleep conditions).

procal reduction in stimulus-related activation of the thalamus [67].

4.2. Increased pain ratings after sleep restriction

Sleep deprived subjects in our study were more sensitive to the applied laser stimuli and showed higher ratings (+30%) compared to the habitual sleep condition. We draw attention to the fact that due to the indirect nature of actigraphy used to differentiate periods of sleep from periods of wakefulness the extent of sleep restriction may have been overestimated. The same impact of reduced sleep on pain perception has recently been shown in a representative epidemiological study in the general population of the US with minimal spontaneous pain at 7–9 h of sleep and subjects reporting longer periods of pain (+30%) on a day following a night of <6 h of sleep (National Study of Daily Experiences [16]). Moreover, previous night sleep duration was the strongest predictor for the actual daily pain duration. Generally, sleep restriction and, in particular, partial sleep restriction lower pain thresholds and make subjects more sensitive to noxious stimuli (e.g. [33,63,70]).

4.3. Dissociation between LEPs and pain ratings following sleep restriction

The question arises, whether an increase of pain ratings after sleep restriction may be attributed to either sensory and/or perceptual amplification. A correlation between subjective pain and laser evoked cerebral responses could be shown in healthy volunteers and patients whereupon larger LEPs are generally associated with an increase of subjective pain perception [7,57]. This association is also apparent in this study (see Fig. 5). Basically, in both sleep conditions lower ratings are linked with smaller amplitudes with regression lines of similar slopes (N2–P2). However, across conditions this association becomes segregated by almost a factor of 2 by sleep restriction: amplitudes of the LEP (both over temporal cortex and vertex) were smaller following sleep restriction, whilst pain ratings were increased similar to the segregation observed in neuropathic pain patients [21] (but opposite to the segregation observed in borderline personality disorder [57,58]). Thus, the increase of pain sensitivity likely results from perceptual amplification, i.e. from postprocessing of nociceptive input, rather than sensory amplification since LEP amplitudes were not increased.

4.4. Attentional modulation of pain and nociceptive processing and impaired cognitive performance

One cardinal feature of sleep restriction is diminished alertness. Pain and concomitant evoked potential were modulated by attentional state as has been described previously, and thus our results replicate former studies that could give evidence of attentional

Table 1
Two-way ANOVA for pain ratings (VAS) and laser-evoked potentials (N1, N2–P2).

	Sleep condition		Attentional focus		Interaction	
	$F_{1,9}$	p-Value	$F_{2,18}$	p-Value	$F_{2,36}$	p-Value
VAS	4.07	0.07	6.93	<0.01	4.38	<0.05
N1	5.37	<0.05	2.45	0.12	1.06	0.37
N2–P2	9.96	<0.02	12.04	<0.001	1.05	0.37

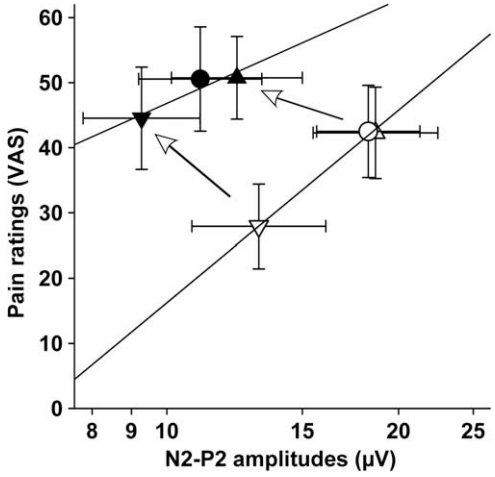

Fig. 5. N2–P2 amplitudes vs. pain ratings. Higher LEP amplitudes were associated with higher pain ratings within the two sleep conditions. Following partial sleep restriction stimuli were rated as more painful although amplitudes were consistently smaller for all three attentional conditions, leading to a leftward/upward shift of the regression line. Open symbols: habitual sleep; filled symbols: sleep restriction. Triangle down: distracted; circle: neutral; triangle up: focused.

modulation of pain experience [2,20,21,38,43,47,77] and the analgesic effect of distraction [5,28,56]. This may differ for tonic pain stimulation, and differentiated results have been published for sustained cold pressor pain. These investigations have found the same effects of attention/distraction in the early stages of cold pain, but different or opposite results for late stages of sustained cold pain, suggesting that distraction may not be functional during that stage. Rather attention was effective to suppress pain explained by cognitive strategies [42,44,68]. Notably, the range of attentional modulation was strongly reduced after sleep restriction compared to normal sleep. This finding suggests a profound difficulty for sleep deprived subjects to adequately allocate attentional resources including disturbances of working memory, which has been reported frequently [8,9,61,72]. We propose that after sleep restriction allocation of attention is also impaired in pain and nociceptive processing, i.e. subjects exhibit a reduced capacity to adequately attend to or disengage from pain.

Another neurobehavioral deficit, reduced cognitive performance is well established, and results from short-term as well as long-term sleep restriction, which was already shown in the first study of long-term sleep restriction in humans [46]. Simple task performance as well as complex task performance is impaired, as reflected by simple reaction time tests [17,69] and complex tests such as working memory, speech articulation, language, logical reasoning, creative thinking and planning, decision making, and judgement [29,30,61,66]. Our study revealed a diminished cognitive performance (mental arithmetics) following sleep restriction. In contrast, a sensory decision task (intensity discrimination) that did not involve working memory was not affected at all.

4.5. Possible mechanisms of pain amplification following sleep restriction

Increased pain ratings following sleep restriction may result from affective modulation or an increase in perceived aversiveness, and negative mood can lead to enhanced pain ratings [78] (for review on emotional modulation, see [31]). In fact, mood appears to be substantially decremented by sleep restriction [12,25,53]. Although we did not collect data on mood states an impact of mood changes after one night of sleep reduction appears unlikely as shown previously by Haack and Mullinton, who reported that only repeated sleep restriction elicited substantial mood changes [25]. Moreover, mood in itself is not sufficient to explain the changes of pain and nociceptive processing after sleep restriction, and the relationship of pain and mood was fundamentally opposite to our findings after sleep restriction in several important clinical examples. Negative mood was accompanied by decreased pain rating in patients with depression [36,37] posttraumatic stress disorder [23], and borderline personality disorder [57,58]. In contrast, mood improvement following sleep restriction in patients with major depression was accompanied by increased pain sensitivity and augmented pain complaints [34]. Thus we dismiss mood changes as a cause of altered pain perception.

The dissociation between LEP decrease and pain rating increase suggests an intracortical amplification process. We propose that this amplification process results from reduced top-down control of the pain processing possibly originating in frontal areas of the brain, in particular in the dorsolateral prefrontal cortex (DLPFC) [45,48,73,74]. Hyperactivity of frontal brain areas was found e.g. in patients with major depression [4] or in patients with borderline personality disorder [57,58], and states of hyperalgesia with DLPFC activity negatively correlating with perceived pain intensity and unpleasantness [40], as a mechanism of intracortical pain inhibition. Recent data by Bastuji and colleagues also suggest a sleep-related role for prefrontal cortex in intracortical pain control [3].

4.6. Conclusions and outlook

We propose that sleep restriction may lead to a reduced capacity of top-down pain control accompanied by reduced allocation of attentional resources. This finding suggests a cortical amplification of nociceptive signalling despite reduced ascending input reflected by reduced LEP amplitudes. It is noteworthy, however, that these frontal brain areas serve more general purposes and have a role in stimulus discrimination and response selection independent of the sensory modality of a stimulus suggesting that also processing of non-nociceptive signals may be impaired [15,26,27]. Generally, reduced prefrontal control may result in a higher frequency of pain complaints in normal subjects and in patients [16,35,54,62]. In pain patients in particular, who often suffer from pain-related sleep disturbance this may contribute to a positive feedback circle further exaggerating their pain complaints.

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