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Sleep restriction does not potentiate nocebo-induced changes in pain and cortical potentials

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Abstract

Background: The increased pain sensitivity following reduced sleep may be related to changes in cortical processing of nociceptive stimuli. Expectations shape pain perception and can inhibit (placebo) or enhance (nocebo) pain. Sleep restriction appears to enhance placebo responses; however, whether sleep restriction also affects nocebo responses remains unknown. The aim of the present study was to determine whether sleep restriction facilitates nocebo-induced changes in pain and pain-evoked cortical potentials.

Methods: In an experimental study with a crossover design, the sensitivity to electrically induced pain was determined in 53 nurses under two sleep conditions, after habitual sleep and after two consecutive nights at work. Nocebo was induced by conditioning one-third of the pain stimuli. Pain-elicited cortical event-related potentials were recorded by electroencephalography (EEG). Data were analysed both in the time domain (N2P2 amplitude) and in the time–frequency domain (ERP magnitude). Sleepiness and vigilance were also assessed.

Results: Both nocebo alone and sleep restriction alone increased the sensitivity to electrically induced pain. However, no interaction effect was found. Moreover, the magnitude of the pain-elicited responses increased after sleep restriction and decreased after nocebo expectation, suggesting that nocebo is probably not an underlying mechanism for the commonly observed hyperalgesia induced by sleep restriction.

Conclusions: The present work addresses whether sleep restriction, known to increase the sensitivity of the pain system, facilitates nocebo-induced hyperalgesia. Our findings suggest that this is not the case, indicating that the increased sensitivity of the pain system following nocebo and sleep restriction are mediated by different cortical mechanisms.

1 | INTRODUCTION

Sleep disturbances and experimentally induced sleep restriction have been associated with exacerbations of chronic pain and with increased psychophysical responses to painful stimulation (Finan, Goodin, & Smith, 2013; Schrimpf et al., 2015). Despite extensive research, the underlying mechanisms responsible for sleep restriction-induced hyperalgesia remain elusive. Sleep restriction has been associated with negative mood changes (Haack & Mullington, 2005; Simon et al., 2015), which have been reported to negatively influence both sleep and pain (O'Brien et al., 2010). Experimental and clinical pain studies have shown that pain reports and levels of negative emotions are highly

correlated (Frot, Feine, Feine, & Bushnell, 2004; Riley III, Robinson, Wade, Myers, & Price, 2001). Thus, the increased sensitivity of the pain system following sleep restriction may rely on changes in the affective processing of painful stimuli.

Nocebo may be defined as the experience of negative symptoms occurring in response to psychological phenomena, such as conditioning and expectations (Webster, Weinman, & Rubin, 2016), and has been associated with increased pain and worsening of symptoms (Atlas & Wager, 2012; Benedetti, Lanotte, Lopiano, & Colloca, 2007; Petersen et al., 2014). Placebo and nocebo share several common mechanisms, for example, conditioning and expectations (Kleine-Borgmann & Bingel, 2018). Sleep restriction potentiates placebo analgesia (Chouchou, Chauny, Rainville, & Lavigne, 2015), but it is unknown whether sleep restriction affects nocebo. It does, however, seem plausible. First, sleep restriction affects the processing of both positive and negative aspects of the emotional spectrum (Goldstein & Walker, 2014). Moreover, studies of nocebo procedures have shown altered activity in the endogenous pain modulatory system (Bingel et al., 2011; Scott et al., 2008), and increased activity of the affective–cognitive (medial) pain system (Kong et al., 2008). Thus, sleep restriction-induced changes in affective–cognitive processing may be one potential explanation for sleep restriction-induced hyperalgesia.

The brain mechanisms underlying altered pain processing following both sleep restriction and nocebo are largely unknown. Following nocebo expectation there seemed to be a correlation between subjective pain and pain-elicited cortical responses to laser stimuli (Lorenz et al., 2005; Pazzaglia, Testani, Giordano, Padua, & Valeriani, 2016). Following sleep restriction, however, there seems to be a dissociation between subjective pain (which is increased) and pain-elicited cortical responses (which are decreased or unchanged) (Matre, Hu, et al., 2015; Ødegård et al., 2015; Schuh-Hofer, Baumgartner, & Treede, 2015; Tiede et al., 2010). When analysed in the time–frequency domain, pain-elicited responses also correlated with increases in sleep restriction-induced subjective pain (Matre, Hu, et al., 2015). Thus, a comprehensive analysis of nocebo responses analysed with time-domain averaging and time–frequency domain following sleep restriction appears to be lacking and warranted, and such an analysis may elucidate potential mechanisms involved in pain hyperalgesia following sleep restriction.

The overall aim of the present study was to determine whether sleep restriction potentiates nocebo-induced changes in subjective pain and pain-evoked cortical potentials. Three hypotheses were tested: (a) Sleep restriction causes hyperalgesia; (b) Nocebo causes hyperalgesia; and (c) Sleep restriction potentiates nocebo-induced hyperalgesia. Here, hyperalgesia is conceptualized as enhanced subjective pain and/or enhanced amplitude of cortical potentials.

2 | METHODS

2.1 | Subjects

Participants were recruited by wall postings or by brief bulletins on the intranet pages at major hospitals in the greater Oslo area. Fifty-eight nurses volunteered for the experiment. Five subjects withdrew before the first experimental day, 53 subjects with a mean age of 31.6 years ($SD = 9.0$; range 24–57; 41 women) participated in the first sleep condition, and 40 subjects participated in both sleep conditions. Of the 13 subjects withdrawing after the first sleep condition, 11 withdrew voluntarily and 2 were excluded due to pregnancy. Despite an unbalanced data set, data from all 53 subjects were analysed since complete case analysis is generally assumed to reduce the robustness of the estimates (Fitzmaurice, Laird, & Ware, 2011).

All subjects reported being healthy. The exclusion criteria were pain with an intensity ≥3 on a numerical rating scale from 0 to 10 with the endpoints "no pain" and "worst imaginable pain" that lasted ≥3 months during the last 2 years, having psychiatric, neurologic, heart or lung disease (well-regulated asthma allowed), headache of moderate intensity for an average of >2 days per month, regular use of over-the-counter analgesics, hypertension (>160/110 mmHg), being pregnant or breast feeding.

All participants received written information and signed an informed consent form. The study was approved by the Norwegian Regional Committee for Medical Research Ethics (approval number 2012/199).

2.2 | Design

The design was a paired crossover study with block randomization. The protocol was performed under two sleep conditions: after at least two nights of habitual sleep (HS condition) and after two consecutive nights at work (NSW condition). Except for three subjects who had their last night shift 3 days before the habitual sleep condition, all subjects had more than four nights with habitual sleep before the experiment, reducing the potential impact of circadian disruption. The participants were instructed to abstain from alcohol 24 hr prior to the laboratory experiment, which took place in the morning, starting between 8 and 9 a.m. In the NSW condition, the subjects came directly to the laboratory from work. The protocol consisted of assessing responses to several pain stimuli, of which data on pressure pain, thermal pain, electrical pain and pain inhibition have been previously published (Matre, Knardahl, & Nilsen, 2017). The novel data in the present study were the inclusion of nocebo and the assessment of event-related potentials.

2.3 | Sleep and sleepiness measurements

At inclusion, daytime sleepiness was measured with the Epworth Sleepiness Scale (ESS) (Johns, 1991). For the 24 hr before each experiment, sleep was monitored by a sleep diary and by a triaxial accelerometer (actigraphy) worn on the non-dominant ankle (ActiSleep, Actigraph LLC, Pensacola, Florida). The sleep diary was smartphone-based (paper based if the subject did not own a smartphone). In the sleep diary, subjects entered bedtime ("lights off"), rise time ("lights on") and naps. Actigraphy-based sleep analysis was performed by the Cole-Kripke algorithm (Actilife software v. 6.12.0, actigraphcorp.com). Sleepiness was reported on the 1–9 Karolinska sleepiness scale (KSS) with the endpoints 1 ("extremely alert") and 9 ("very sleepy", "great effort to keep awake" and "fighting sleep") (Akerstedt & Gillberg, 1990). Vigilance was obtained by a computerized version of the 10-min psychomotor vigilance test (PVT) (Basner & Dinges, 2011) (custom written C++ program, National Institute of Occupational Health, Norway).

2.4 | Painful electrical stimulation

High-density electrical stimulation was delivered through a platinum electrode (diameter 0.2 mm) protruding 0.2 mm from the surface of a polyoxymethylene (POM) frame (custom made at the National Institute of Occupational Health, Oslo, Norway) (Matre, Hu, et al., 2015). The pin electrode served as the cathode. Double-adhesive tape attached the electrode to the randomized left or right volar forearm skin approximately 10 mm medial to half the distance between the insertion point of the biceps brachii tendon and the distal end of ulna. A conductive Velcro-strap (Alpine Biomed ApS, Skovlunde, Denmark) soaked in isotonic NaCl served as the anode and was placed on the ipsilateral upper arm 5 cm proximal to the cubital fossa. A constant current stimulator (DS7A and DG2A, Digitimer, Hertfordshire, England) delivered the electrical stimuli. Each stimulus consisted of two unipolar pulses with a 0.5-ms duration and a 10-ms inter-pulse interval (Mouraux, Iannetti, & Plaghki, 2010).

2.5 | EEG recording

Electroencephalographic (EEG) registrations were made from 32 electrodes placed according to the international 10–20 system using a soft electrode cap matching the subject's head size (actiCAP, Brain Products GmbH, Gilching, Germany). During recording, the common reference electrode was FCz. The continuous EEG signal was amplified, filtered (0.53–100 Hz) and sampled at 2 kHz (QuickAmp 40-channel amplifier and Brain Vision Recorder, Brain Products GmbH, Gilching, Germany). The impedance was kept below 20 kΩ. Ocular movements and eye blinks were monitored by two surface electrodes placed at the upper left (VEOG) and lower right (HEOG) side of the eyes.

2.6 | Procedure

Subjects were familiarized with the procedures on a pre-test session two days before the first test session. During the pre-test, each subject's pain threshold (PT) was determined by a ladder sequence consisting of three ascending series of stimuli (start: 0 mA; step-wise increase: 0.1 mA). The lowest stimulus rated painful by the subject defined the PT. The PT was calculated as the mean of the last two stimuli. During the pretest, three different visual warning symbols signalling stimulus intensity were introduced to the subjects. The stimulus with an intensity at 2 × PT (intensity A) was preceded by a circle, an intensity at 3 × PT (intensity B) was preceded by a rectangle and an intensity at 4 × PT (intensity C) was preceded by a triangle. A computer screen placed approximately 1 m in front of the subjects displayed the warning symbol for 2 s. The inter-stimulus interval varied randomly between 25 and 60 s. The warning symbol was presented between 5 and 35 s before the electrical stimulus. A total of 60 stimuli were presented and were equally divided between the three stimulus intensities.

The two test sessions were 38.1 ± 39.6 days apart (mean ± *SD*) and were identical except for the sleep condition (HS vs. NSW). It was difficult for some of our participants to fit the experimental sessions into their shift rotation, resulting in a relatively large variation in days between the test sessions. The experiment started by filling out the KSS questionnaire. After 5 min of rest in the sitting position, blood pressure was measured three times (Dinamap V100, GE Healtcare, www.gehealthcare.com), followed by the 10-min PVT. Thereafter, EEG recording electrodes were mounted, and several experimental pain stimuli were delivered in this sequence: pressure pain, 60 electrical pain stimuli, heat pain and finally heat pain in parallel with cold pain. Pain scores were obtained after each stimulation using a computerized 10-cm visual analogue scale (VAS) with the endpoints "not painful" and "worst imaginable pain". All participants were tested by one of two female experimenters who were blinded with respect to the sleep condition. All instructions followed a standardized written protocol.

2.7 | Induction of nocebo

Nocebo was induced by conditioning (Price, Finniss, & Benedetti, 2008). During the test sessions, one-third of the intensity A-stimuli were preceded by a rectangle (falsely signalling intensity B) and one-third of the intensity B-stimuli were preceded by a triangle (falsely signalling intensity C). These trials constituted the nocebo condition. The remaining two-thirds of the intensity A and B stimuli presentations constituted the control condition.

2.8 | Data analysis

Only the results from the electrical pain stimuli with nocebo expectations were analysed in the present manuscript. The results from the pressure pain, thermal pain and electrical stimuli without nocebo expectations were published in Matre et al. (2017).

Total sleep time (TST), number of awakenings (NA) and wakefulness after sleep onset (WASO) were calculated based on the actigraphy measurements and times for "lights off" and "lights on". Seven subjects practised napping, and for these subjects, the napping length was added to the total sleep time before analysis. Statistical analysis on the psychomotor vigilance test (PVT) was performed on mean inverse reaction time, which has been shown to be particularly sensitive to sleep restriction (Basner & Dinges, 2011).

Electrical pain scores were averaged for each of the eight experimental conditions (2 sleep × 2 expectancy × 2 intensity). Intensity C-stimuli pain scores were excluded from the analysis, since these did not have a nocebo comparison.

A pseudo-randomized order between conditions was applied, inducing no systematic difference between conditions. There was no systematic difference between participants who started the experiment with sleep restriction versus habitual sleep (effects of sex: $p = .32$; age: $p = .26$).

2.9 | EEG preprocessing

EEG data were available from 91 of the 93 experiments (40 subjects × 2 sleep conditions + 13 subjects × 1 sleep condition). EEG data were extracted from nine electrodes: three central electrodes Fz, Cz and Pz, three ipsilateral (i) electrodes F3/4i, C3/4i and P3/4i, and three contralateral (c) electrodes F3/4c, C3/4c and P3/4c (international 10–20 system). The central and contralateral electrodes were included as previous research on sleep restriction has primarily focused on the central and contralateral electrodes (Matre, Hu, et al., 2015). The ipsilateral electrodes were included as the P2 component is generated in deeper brain structures, such as the ACC, and related to the cognitive and affective components of pain (Bentley, Youell, & Jones, 2002; Bromm & Lorenz, 1998). The presence of increased affective ratings following sleep restriction has been previously demonstrated (Schuh-Hofer et al., 2015). Since we are more interested in regional changes, rather than the ERP response from each single electrode, an analysis was performed on the mean N2P2 magnitude and the mean ERP magnitude across the frontocentral region and the parietal region. The nine electrodes were therefore reduced to a frontocentral (FC) region (F3/4i, F3/4c, Fz, C3/4i, C3/4c and Cz) and a parietal (P) region (P3/4i, P3/4c and Pz). Recordings were downsampled to 512 Hz, re-referenced to the TP9 and TP10 electrode means, corrected for blinking by independent component analysis and exported to MATLAB format (Brain Vision Analyzer 2.0, Brain Products GmbH, Gilching, Germany). Segments with values exceeding ± 150 μV were automatically rejected (EEGLAB v.13.6.5b), resulting in 10.6% of single-trial responses being discarded. The data related to stimulus intensity C were not included in the analysis, since all intensity C-stimulations were correctly signalled and thereby not related to the nocebo condition, leaving eight experimental conditions (2 sleep × 2 nocebo × 2 intensity). The evoked responses were analysed in the time-domain and in the time–frequency domain.

2.10 | Time-domain analysis

For the time-domain analysis, across-trial average responses were generated for each condition and electrode. A semi-automatic search was performed to identify the maximum negative peak N1 between 50 and 200 ms at the contralateral T7/T8c electrode, as well as the maximum negative peak between 50 and 200 ms (N2) and the maximum positive peak between 150 and 500 ms (P2) at the remaining nine electrodes (custom written MATLAB script). The N2P2 peak-to-peak amplitude was calculated (Figure 1 top). Visual inspection of N1 and N2P2 led to discarding 27% of the available N1 recordings and 11% of the available N2P2 recordings. The rationale for discarding recordings was a low signal-to-noise ratio or contamination by EMG, making validation of the peak amplitudes uncertain.

2.11 | Time–frequency domain analysis

For the time–frequency analysis, segmented data were analysed by means of custom written MATLAB scripts (Matre, Hu, et al., 2015). The power spectral density of each epoch was calculated using the windowed Fourier transform (200-ms Hanning window) and averaged across trials to obtain the time–frequency representations for each subject and condition. The magnitude of event-related changes in oscillation amplitude was determined as the percentage change in power for each time–frequency (TF) point relative to a pre-stimulus reference interval (−900 to −100 ms) (Zhang, Hu, Hung, Mouraux, & Iannetti, 2012). The time–frequency analysis revealed three clusters with significant changes in magnitude compared to the pre-stimulus reference interval. As in a previous study from our laboratory (Matre et al., 2015), the most significant of these clusters captured an early low-frequency response corresponding to the N2P2 complex detected in the time domain. A rectangular search area was defined to capture this cluster (1–400 ms/1–25 Hz) (white dashed rectangle in Figure 1, bottom). Furthermore, a significant late event-related desynchronization (ERD) cluster was observed in the alpha and beta frequency ranges (8–13 and 14–20 Hz; 200–800 ms post-stimulus) and in the

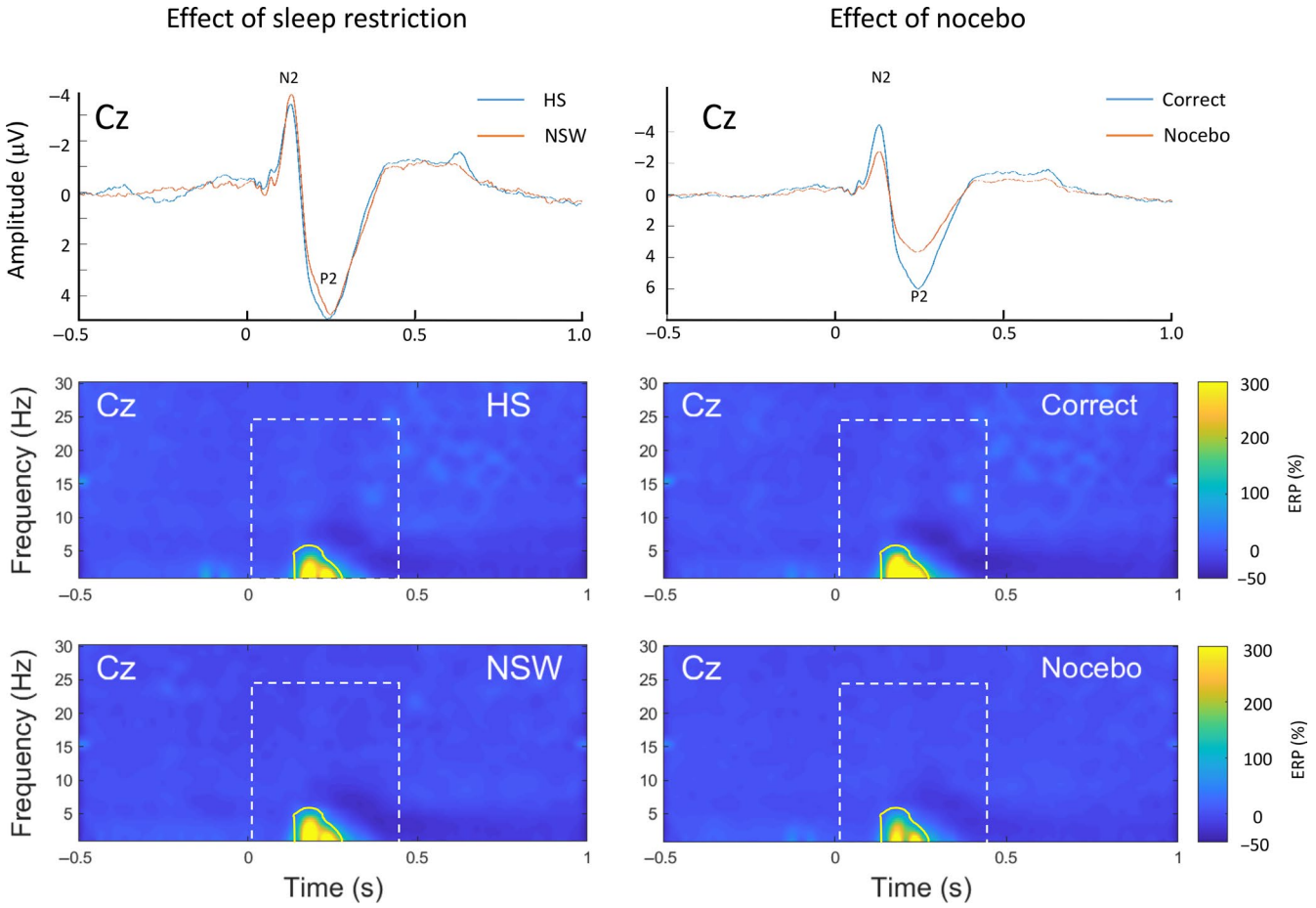

FIGURE 1 Top: Time-domain average from electrode Cz with the effect of sleep restriction (left) and nocebo (right). Bottom: Time–frequency domain grand average from electrode Cz with the effect of sleep condition and nocebo. White dashed rectangle indicates 1–400 ms/1–25 Hz search area. Yellow line indicates exact region of interest. HS, Habitual sleep; NSW, Night shift work

gamma frequency range (33–60 Hz; 190–470 ms post-stimulus). The magnitudes of the percentage change in power within these clusters did not vary with sleep (data not shown) and were therefore not further analysed. Neither was there a main effect of sleep condition ($p > .24$) or nocebo expectation ($p > .16$) on the pre-stimulus α-level, which was also not further analysed.

Significant TF points determined exact regions of interest by a combination of bootstrapping (1,000 times) and a paired *t* test ($p < .01$ uncorrected) (Durka, Zygierewicz, Klekowicz, Ginter, & Blinowska, 2004). It was decided a priori that to be considered, data points had to form a cluster with bandwidths of at least 10 Hz and 50 ms. This was visually identified. The significant cluster for electrode Cz is shown in Figure 1 (time–frequency histograms, yellow line). The clusters differed slightly in size and shape between electrodes and varied between 1,010 and 2,929 data points across electrodes. The mean percent change across the significant data points for an electrode relative to the reference interval (ERP) was then calculated for each electrode.

2.12 | Statistics

The primary a priori hypothesis was that sleep restriction would facilitate pro-nociceptive mechanisms, as tested by the nocebo condition. In other words, the sleep × nocebo interaction was our primary interest. Unless otherwise noted, all analyses were performed by linear mixed models (LMM) with an unstructured covariance structure. The primary fixed factors for each outcome measure were sleep condition (HS vs. NSW), nocebo (vs. control), and the sleep × nocebo interaction. In addition, stimulus intensity (A vs. B) and the sleep × intensity interaction were included as fixed factors for model adjustment, since pain and pain-elicited potentials are typically sensitive to changes in stimulus intensity. Non-significant interaction effects ($p > .05$) were removed from the model. The outcome measures were pain ratings of the electrical pinprick stimuli and electrophysiological variables analysed in the time-domain (N1 peak amplitude and N2P2 peak-to-peak amplitude) and in the time–frequency domain (ERP magnitude). For the N2P2 and ERP magnitude, one

analysis was performed for the frontocentral region and one for the parietal region. The analyses for single electrodes are shown in the supplementary material.

All LMM analyses followed the same general procedure. First, based on minimizing the Akaike information criterion (AIC), it was determined whether sleep condition, nocebo condition or stimulus intensity should be included as a random slope in the model. Second, sleep, nocebo and the sleep × nocebo interaction were entered as fixed factors. Third, the sleep × intensity interaction was tested for significance.

The intercept was allowed to randomly vary in all models. Each final model was calculated with restricted maximum likelihood (REML) estimation. The fit of each model was tested by visual observation of the Q–Q plot of the residuals as an indicator of normality.

A paired comparison between HS and NSW sleep conditions was performed on the sleep variables by the non-parametric Wilcoxon test, since most of the variables were probably non-normally distributed (visual inspection of the histogram).

Statistical analyses were performed with Stata v.13.

3 | RESULTS

3.1 | Sleep parameters and blood pressure

The Epworth Sleepiness Scale scores were available for 40 subjects ($M = 7.3$, $SD = 3.62$) and ranged from 1 to 16. Seven subjects had a score of 11 or greater, indicating high daytime sleepiness. Subjective sleepiness (KSS) was rated higher and reaction time was longer (measured by PVT) after NSW than after HS. Actigraphy was successfully recorded before both sleep conditions in 36 subjects, before one of the sleep conditions in 15 subjects, and not at all in 2 subjects, due to technical difficulties. Fewer awakenings were measured after NSW compared with after HS, whereas wakefulness after sleep onset (WASO) was not different between sleep conditions. The total sleep time over the previous 24 hr was approximately 1 hr shorter in the NSW condition. Sleep parameter statistics are presented in Table 1. Subjects were normotensive (mean systolic blood pressure was 114.8 (*SD* 9.6) mmHg and mean diastolic blood pressure was 68.7 (*SD* 7.7) mmHg).

3.2 | Pain scores

Electrically induced pinprick pain scores were significantly associated with sleep condition ($p = .01$), nocebo ($p < .001$) and stimulus intensity ($p < .001$; Table 2). Importantly, there was no sleep × nocebo interaction ($p = .60$). Pain ratings increased by 19% from 1.9 ± 1.5 cm after HS to 2.4 ± 1.5 cm after NSW sleep restriction. The estimated effect size for sleep was 0.39 cm (Table 2). Pain ratings increased by 20% with nocebo of higher stimulus intensity (nocebo), from 2.0 ± 1.4 cm during control conditions to 2.3 ± 1.6 cm during nocebo conditions. The estimated effect size for nocebo was 0.36 cm (Table 2). Figure 2 shows how pain ratings

TABLE 1 Descriptive statistics of subjective and objective sleepiness and actigraph-based measurement of total sleep time, number of awakenings and wakefulness after sleep onset

	HS		NSW			
	Mean	***SD***	**Mean**	***SD***	***z***	***p***
Subjective sleepiness, KSS	4.1	1.7	6.9	1.0	−5.32	**<.001**
Reaction time (s)	0.38	2.34	0.41	1.80	3.05	**.002**
Total sleep time (TST) (hr)	7.5	1.3	6.5	1.5	3.14	**.002**
Number of awakenings (NA)	6.1	4.9	4.6	3.6	2.71	**.007**
Wakefulness after sleep onset (WASO) (min)	13.6	12.0	14.3	12.3	0.10	.918

Note: Values are mean ± standard deviation based on 40 subjects participating in both sleep conditions. HS, Habitual sleep; NSW, Night-shift work. KSS was measured by the Karolinska Sleepiness Scale (1–9). Reaction time was measured by the 10-min PVT test. Total sleep time (TST), number of awakenings (NA) and wakefulness after sleep onset (WASO) was calculated based on actigraphy measurements (Cole-Kripke algorithm) adjusted with lights-off and lights-on times from the diary, and adding self-reported naps. *p* values are from the Wilcoxon signed rank test.

TABLE 2 Statistical summary after linear mixed models with electrical pain scores as dependent variable

	Coefficient (VAS)	95% CI (VAS)		*p*-value
Sleep	.39	0.08	0.70	**.01**
Nocebo	.36	0.23	0.50	**<.001**
Stimulus intensity	.92	0.67	1.17	**<.001**
Sleep × nocebo	.06	−0.15	0.26	.60

Abbreviations: CI, confidence interval; VAS, visual analogue scale, 0–10 cm.
Bold values were signifiant at the α=0.05 level.

were changed by sleep and nocebo. Although not a primary hypothesis, the data indicated an increase in pain ratings by 59.6% from intensity A (1.66 ± 1.14 cm) to intensity B (2.5 ± 1.68 cm) ($p < .001$), with an estimated effect size of 0.92 cm. There was no sleep × intensity interaction ($p = .13$).

3.3 | Time-domain evoked responses

The mean N2P2 amplitude in the frontocentral ROI was almost twice the N2P2 amplitude found in the parietal ROI (Table 3). The N2 latency varied from 125.5 to 146.7 ms between the nine electrodes (Table S2). P2 latency varied from 250.1 to 286.9 ms (Table S2).

The temporal (T7/8) N1 amplitude did not change after NSW sleep restriction ($p = .83$) or nocebo ($p = .22$). In the parietal region, the mean N2P2 amplitude just passed below the significance threshold after NSW sleep restriction ($p = .06$; Tables 3 and 5A). In the frontocentral region, sleep restriction did not change the mean N2P2 amplitude ($p = .296$; Tables 3 and 5A). Nocebo demonstrated an opposite anatomical distribution, eliciting a significantly decreased frontocentral response ($p = .002$) but not a parietal response ($p = .392$; Table 5A). Importantly, there was no sleep × nocebo interaction in any region ($p > .41$). Although not a hypothesis of primary interest, N2P2 amplitude increased significantly with stimulus intensity in the frontocentral region ($p = .001$) and showed a tendency towards significance in the parietal region ($p = .083$; Table 5A). There was no sleep x intensity interaction in any region ($p > .24$, data not shown).

The results from single electrode analyses are shown in supplementary Table S1A (descriptives) and Table S4A (statistics).

3.4 | ERP response, time–frequency domain

ERP responses in the frontocentral region, as measured in % change of the ERP magnitude relative to the pre-stimulus interval, were approximately twice the magnitude as ERP responses in the parietal region (Table 4).

NSW sleep restriction significantly increased the ERP magnitude in both the frontocentral ($p = .01$) and the parietal region ($p = .005$; Table 5B). Nocebo did not change the ERP magnitude in either region ($p > .267$; Table 5B).

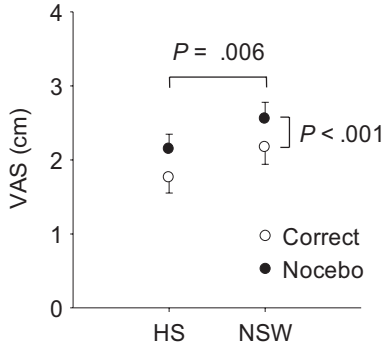

FIGURE 2 Electrical pain by sleep and nocebo conditions. There was a main effect of sleep ($p = .006$), and a main effect of nocebo ($p < .001$), but no sleep × nocebo interaction ($p = .6$). Values are estimated marginal means

TABLE 3 Descriptive statistics N1 and N2P2 amplitude by sleep restriction (A) and expectation (B)

	HS		NSW		Difference from HS	
	Mean (μV)	***SD* (μV)**	**Mean (μV)**	***SD* (μV)**	**(μV)**	**(%)**
A. Effect of sleep restriction						
N1						
T7/8c	−17.1	9.2	−16.4	9.0	0.7	−3.9
N2P2						
FC	27.8	11.0	30.5	11.6	2.6	9.3
P	16.8	6.2	18.1	6.4	1.3	7.6
	Control		**Nocebo**		**Difference from control**	
	Mean (μV)	**SD (μV)**	**Mean (μV)**	**SD (μV)**	**(μV)**	**(%)**
B. Effect of nocebo						
N1						
T7/8c	−17.0	9.3	−16.6	8.9	0.4	−2.4
N2P2						
FC	29.9	11.5	28.4	11.2	−1.6	−5.2
P	17.6	6.5	17.2	6.3	−0.4	−2.4

Abbreviations: FC, frontocentral electrodes; HS, habitual sleep; NSW, nightshift work; P, parietal electrodes.

TABLE 4 Descriptive statistics, mean and standard deviation (*SD*), of ERP magnitude by sleep (A) and nocebo (B) in percent difference from pre-stimulus interval

	HS		NSW		Difference from HS	
	Mean (%)	***SD* (%)**	**Mean (%)**	***SD* (%)**	**(%)**	**(% of HS)**
A. Effect of sleep restriction						
FC	117.5	111.8	149.9	135.8	32.4	27.6
P	48.6	66.0	70.6	85.2	22.0	45.4
	Control		**Nocebo**		**Difference from control**	
	Mean (%)	***SD* (%)**	**Mean (%)**	***SD* (%)**	**(%)**	**(% of control)**
B. Effect of nocebo						
FC	134.4	119.4	122.1	118.3	−12.4	−9.2
P	58.0	74.3	52.8	71.9	−5.2	−9.0

Abbreviations: FC, frontocentral electrodes; HS, habitual sleep; NSW, nightshift work; P, parietal electrodes.
Bold values were signifiant at the α=0.05 level.

TABLE 5 Statistical summary after linear mixed models with N2P2 peak amplitude and ERP magnitude as dependent variables

	A. N2P2				B.ERP			
	Coef.	**95% Conf.**	**interval**	***p*-value**	**Coef.**	**95% Conf.**	**interval**	***p*-value**
FC								
Sleep condition	1.27	−1.11	3.65	.296	35.0	8.2	61.8	**.010**
Nocebo	−1.92	−3.11	−0.72	**.002**	−10.8	−29.8	8.3	.267
Stimulus intensity	1.42	0.57	2.27	**.001**	9.6	−3.0	22.1	.136
Sleep × nocebo	0.71	−0.98	2.41	.410	4.4	−21.0	29.7	.734
P								
Sleep condition	1.18	−0.05	2.40	.060	23.4	7.0	39.7	**.005**
Nocebo	−0.40	−1.33	0.52	.392	−7.3	−22.0	7.3	.326
Stimulus intensity	0.58	−0.08	1.24	.083	4.0	−5.7	13.7	.416
Sleep × nocebo	−0.03	−1.34	1.29	.965	−1.5	−21.1	18.1	.881

Abbreviations: CI, confidence interval; FC, frontocentral electrodes; ERP, event-related potential; P, Parietal electrodes.
Bold values were signifiant at the α=0.05 level.

There was no sleep x nocebo interaction ($p > .734$). The ERP magnitude was not associated with stimulus intensity ($p > .136$; Table 5B). There was no sleep x intensity interaction in any region ($p > .72$, data not shown).

The results from single electrode analyses are shown in supplementary Table S1B (descriptives) and Table S4B (statistics).

4 | DISCUSSION

The main finding of the present study was that sleep restriction did not potentiate nocebo-induced changes in pain or the cortical potentials to painful stimulation. Sleep restriction and nocebo did, however, affect both pain and evoked cortical potentials independently of each other. In the parietal region, sleep restriction induced by night shift work increased cortical potentials, particularly in the time–frequency domain. In the frontocentral region, sleep restriction increased cortical potentials only in the time–frequency domain. Nocebo-induced changes only in the frontocentral region, with decreased pain-elicited cortical potentials in the time domain. Thus, although the hyperalgesia induced by sleep restriction and the hyperalgesia induced by nocebo have comparable effect sizes in changing pain scores (Table 2), the cortical activity evoked by the two phenomena do not appear to be similar. Consequently, in the present experimental set-up, there does not seem to be support for nocebo as one of the underlying mechanisms for the hyperalgesia induced by sleep restriction.

After night work, compared to after habitual sleep, subjective pain scores increased by 19% (mean difference 0.4 cm). This effect size was comparable to other studies on heat pain (26.5% increase) based on data from the same individuals (Matre et al., 2017) and another study on cold pain after night work (28% increase) (Pieh et al., 2018). Similar studies using experimental sleep restriction have shown comparable effect sizes (Azevedo et al., 2011; Matre, Andersen, Knardahl, &

Nilsen, 2016; Matre, Hu, et al., 2015; Schuh-Hofer et al., 2015; Tiede et al., 2010). Subjective pain scores increased by 20% (mean difference 0.30 cm) in the nocebo versus control conditions. This effect size is comparable to other experimental studies of nocebo effects (Aslaksen, Zwarg, Eilertsen, Gorecka, & Bjørkedal, 2015, Babel et al., 2017).

The main aim of the present study was, however, to determine whether sleep restriction potentiated nocebo-induced changes in pain, but this was not supported. The data indicated that expectations of higher pain levels do not explain sleep restriction-related hyperalgesia. This is noteworthy, considering that sleep restriction is associated with negative mood changes (Haack & Mullington, 2005; Simon et al., 2015) and that negative mood may mediate part of the relationship between poor sleep and pain, although to date, these findings only pertain to fibromyalgia patients (O'Brien et al., 2010). Another experimental study, however, suggested that sleep disturbance has a stronger influence on the positive affective system relative to its effect on the negative affective system (Finan et al., 2016). It is likely that nocebo manipulates the latter. Moreover, Krause, Prather, Wager, Lindquist, and Walker (2019) recently found altered processing of nociceptive stimuli at cortical levels following sleep deprivation that were unrelated to mood and anxiety. Future experimental studies investigating whether sleep restriction potentiates nocebo-induced changes in pain should include measures of positive and negative mood, which is a limitation of the present study.

Sleep restriction increased cortical potential magnitude both in the frontocentral and the parietal region, but only when analysed in the time–frequency domain. This confirms and extends previous findings (Matre, Hu, et al., 2015). Thus, it appears that the increased subjective pain after sleep restriction correlates with an increased ERP magnitude over a relatively large region of the brain if the frequency content of the signal is taken into account. Recent findings have suggested that the lower bandwidth frequencies (theta: 4–8 Hz) are a dynamic and reliable indicator of pain perception in response to tonic pain (Gram, Graversen, Olesen, & Drewes, 2015) and in response to phasic laser pain (Tiemann et al., 2015). Interestingly, the time–frequency responses to phasic and tonic pain differ with respect to their topographical representation (Schulz et al., 2015). Within a few minutes of tonic pain, the frontocentral region appeared to demonstrate a dissociation of the subjective coding of the perception of pain and the objective stimulus intensity. Moreover, this dissociation did not occur in response to phasic pain (Schulz et al., 2015). It has previously been suggested that chronic pain involves a shift from sensory processing to the activity of emotional brain circuits (Hashmi et al., 2013). Although speculative, it is possible that the increased activity of the frontocentral region observed in response to the phasic painful stimuli in the present study indicated a gradual shifting of brain circuit activity following sleep restriction.

Contrary to the findings of the time–frequency analysis, the amplitude of the signal (time-domain analysis of N2P2) seemed to be less sensitive to changes in sleep duration. This is consistent with several previous studies that have reported unchanged or even decreased N2P2 responses following sleep restriction (Azevedo et al., 2011; Matre, Hu, et al., 2015; Ødegård et al., 2015; Schuh-Hofer et al., 2015; Tiede et al., 2010). Although not a primary aim of the present study, we also analysed each of the nine electrodes separately. A new finding that emerged was that sleep restriction also increased the response in some of the electrodes in the time-domain (contralateral F3/4 and in ipsilateral and contralateral P3/4; Table S4A).

Nocebo decreased cortical magnitude only in the frontocentral region and only in the time domain. It has been previously shown that a reduced evoked potential amplitude was observed in midline electrodes after placebo-induced analgesia (Wager, Matre, & Casey, 2006). Thus, a possible explanation is that the observed reductions in evoked potential magnitude in both placebo and nocebo conditions reflect a cognitive component related to expectancy, rather than to the actual pain report. In support of this explanation, a PET study has shown that the direction of the response to pain anticipation depends on whether the anticipated painful stimulus is unknown or known. Upon anticipating an unpredictable and unlearned pain stimulus, the activity in the anterior cingulate cortex and the ventromedial prefrontal cortex increased, whereas anticipating a learned pain stimulus resulted in decreased activity in the same structures (Hsieh, Stone-Elander, & Ingvar, 1999). It is likely that the activity in the anterior cingulate cortex and the ventromedial prefrontal cortex contributes to the responses measured by the current frontocentral electrodes, yielding a plausible explanation for the present nocebo-induced reductions in N2P2 and ERP magnitude. The present results on N2P2 are in contradiction to Lorenz et al. (2005), but differences in inducing expectations (predictable vs. unpredictable) may have contributed to this discrepancy. Several other methodological differences between the present findings and those reported by Lorenz et al. (2005) need to be considered. For instance, Lorenz et al. (2005) assessed pain evoked by heat on a 9-point scale and had a skewed distribution of the warning signals: 80% were correctly signalled and 20% were incorrectly signalled. Future studies using imaging technology may elucidate whether the same brain structures are also involved in nocebo expectation.

The present study has some limitations and strengths that should be mentioned. A majority of the subjects (41 of 53) were women, and the potential effect of the menstrual cycle was not taken into account in the analyses. We were not able to control for factors related to circadian rhythm

disruption. Little documentation exists on variation in pain sensitivity due to circadian phase, but one study found only small differences in heat and cold pain sensitivity (Strian, Lautenbacher, Galfe, & Holzl, 1989). Furthermore, although the present article presents results from electrical stimulation only, the total number of pain tests was relatively high, and one cannot exclude carry-over effects between tests. However, this is unlikely to have affected our main finding as the order of the tests was fixed. The level of sleep restriction-induced hyperalgesia and nocebo were generally low, and therefore, the clinical significance of the findings may be small. However, previous findings have suggested that the levels of pain and inflammatory markers increase with more days of partial sleep restriction (Haack, Sanchez, & Mullington 2017). Thus, we believe that the effects we observed in the pain ratings and cortical evoked potentials would continue and indeed further develop with an increasing number of days, making our findings highly relevant. Additionally, the subjects of the present study were adults, representative of the working population, and somewhat older than subjects in many previous experimental sleep restriction studies, which is a strength compared to most experimental studies. Revealing significant effects in such a group increases external validity. Another strength of the present study is the use of a sleep diary verified by actigraphy. The common neurophysiological procedure of replicating responses separately in two blocks was not followed, since in this project, we were looking for differences between experimental conditions, not between individuals.

In conclusion, it seems that although hyperalgesia induced by sleep restriction and by nocebo have relatively comparable effect sizes, the cortical activity evoked by the two phenomena do not appear to be similar. The findings do not support nocebo as one of the underlying mechanisms explaining sleep restriction-induced hyperalgesia.

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SUPPORTING INFORMATION

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