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ORIGINAL ARTICLE

Investigation of pain sensitivity following 3 nights of disrupted sleep in healthy individuals

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Abstract

Background: Poor quality sleep is a common complaint among people with chronic pain. The co-occurrence of poor sleep quality and chronic pain often comes with increased pain intensity, more disability and a higher cost of healthcare. Poor sleep has been suggested to affect measures of peripheral and central pain mechanisms. To date, sleep provocations are the only models proven to affect measures of central pain mechanisms in healthy subjects. However, there are limited studies investigating the effect of several nights of sleep disruption on measures of central pain mechanisms.

Methods: The current study implemented three nights of sleep disruption with three planned awakenings per night in 30 healthy subjects sleeping at home. Pain testing was conducted at the same time of day at baseline and follow-up for each subject. Pressure pain thresholds were assessed bilaterally on the infraspinatus and gastrocnemius muscles. Using handheld pressure algometry, suprathreshold pressure pain sensitivity and area were also investigated on the dominant infraspinatus muscle. Cuff-pressure pain detection and tolerance thresholds, temporal summation of pain and conditioned pain modulation were investigated using cuff-pressure algometry.

Results: Temporal summation of pain was significantly facilitated ($p = 0.022$), suprathreshold pain areas ($p = 0.005$) and intensities ($p < 0.05$) were significantly increased, and all pressure pain thresholds were decreased ($p < 0.005$) after sleep disruption compared to baseline.

Conclusions: The current study found that three consecutive nights of sleep disruption at home induced pressure hyperalgesia and increased measures of pain facilitation in healthy subjects, which is consistent with previous findings.

Significance: Poor quality of sleep is often experienced by patients with chronic pain, with the most common complaint being nightly awakenings. This exploratory study is the first to investigate changes in measures of central and peripheral pain sensitivity in healthy subjects after sleep disruptions for three consecutive nights without any restrictions on total sleep time. The findings

suggest that disruptions to sleep continuity in healthy individuals can induce increased sensitivity to measures of central and peripheral pain sensitization.

1 | INTRODUCTION

Chronic pain is a major health burden, affecting approximately a fifth of the world's population, with considerable negative impacts on quality of life (Arendt-Nielsen et al., 2018; Reid et al., 2011). Additionally, chronic pain is considered a substantial economic burden for society, comparable to the treatment of cancer, diabetes or heart diseases (Gaskin & Richard, 2012).

Increasing evidence suggests that central pain mechanisms, assessed using quantitative sensory testing, are altered in patients with chronic pain (Arendt-Nielsen et al., 2018; Arendt-Nielsen, Skou, et al., 2015; Marcuzzi et al., 2018). Examples of these changes are facilitated temporal summation of pain (TSP) and impaired conditioned modulation of pain (CPM), which are both associated with increased pain (Arendt-Nielsen, Egsgaard, et al., 2015) and poor outcome of standard pain treatments (Petersen, Olesen, et al., 2019). Other common features in patients with chronic pain are referred pain and widespread hyperalgesia, which are also suggested to be driven primarily by central mechanisms (Doménech-García et al., 2016; Laursen et al., 1999).

Poor sleep quality has previously been associated with measures of central pain sensitization (Wei et al., 2018; Wiklund et al., 2020) and commonly co-occurs with pain conditions, reported by up to three-quarters of patients with chronic pain (Sun et al., 2021). Insufficient sleep might contribute to the development and chronification of pain (Haack et al., 2020; Koffel et al., 2016; McBeth et al., 2015; Mork & Nilsen, 2012) and is associated with numerous other health problems such as obesity, cancer and cognitive changes (Blake et al., 2018; Chattu et al., 2018). Sleep disruptions are also known to increase systemic inflammation (Irwin et al., 2016), which leads to sensitization of pain pathways (Ito et al., 2001; Kawasaki et al., 2008; Taiwo & Levine, 1988). Those suffering from poor quality sleep and chronic pain are commonly seen to have increased pain intensity (Dragioti et al., 2018; Larsen et al., 2021), more spreading of pain (Wiklund et al., 2020), reduced functional ability (Naughton et al., 2007) and higher costs of healthcare (Dragioti et al., 2018) compared to those who report good quality sleep.

Experimental models of pain that mimic features of clinical pain allow for investigation of an individual before and after pain arises, which is often not possible when studying patients with chronic pain (Petersen, McPhee, et al., 2019). Many experimental pain models are limited, only provoking changes in the peripheral nervous system (Petersen, McPhee, et al., 2019), and to date, sleep provocations are the only models proven to affect central pain mechanisms (Smith et al., 2007, 2019; Staffe et al., 2019). Patients with chronic pain most frequently report a disrupted sleep pattern (Karaman et al., 2014; Keilani et al., 2018), which has been suggested to be equally as problematic as short sleep duration (Medic et al., 2017) but might not compare to experimental models using total sleep deprivation or sleep restriction (Schuh-Hofer et al., 2013; Simpson et al., 2018; Sivertsen et al., 2015; Staffe et al., 2019). While experimental sleep disruption has previously been linked to signs of central pain sensitization, these studies implemented extensive sleep disruption, inevitably also including some degree of sleep deprivation (Iacovides et al., 2017; Smith et al., 2007, 2019). To date, there is still a lack of evidence on the effect of consecutive nights of sleep disruption as a model for sensitization of central pain mechanisms in a sample of healthy subjects. Therefore, the current study aims to investigate the effect of three consecutive nights of disrupted sleep on assessments of central pain mechanisms and related cognitive factors.

2 | METHODS

Each participant attended an experimental session before and after the three nights with disrupted sleep (baseline and follow-up). In both sessions, participants answered a battery of validated questionnaires followed by pain sensitivity assessments using computer-controlled cuff-pressure algometry and handheld pressure algometry. In the baseline session, the participants were also instructed on the planned awakenings and equipped with the FitBit charge 4 on their nondominant wrist. Furthermore, they completed a baseline entry in the sleep diary. The participants completed the nights with sleep disruption at home and completed a sleep diary entry each morning of the study. An overview of the experimental protocol can be seen in Figure 1.

2.1 | Participants

Thirty healthy participants (15 female) aged 18–45 years were recruited through notices on social media, community boards and forsog.dk. Exclusion was warranted if they reported any of the following: drug or alcohol addiction; current use of medications that might affect the trial (e.g. analgesics and anti-inflammatory drugs); previous or current history of chronic musculoskeletal, neurological,

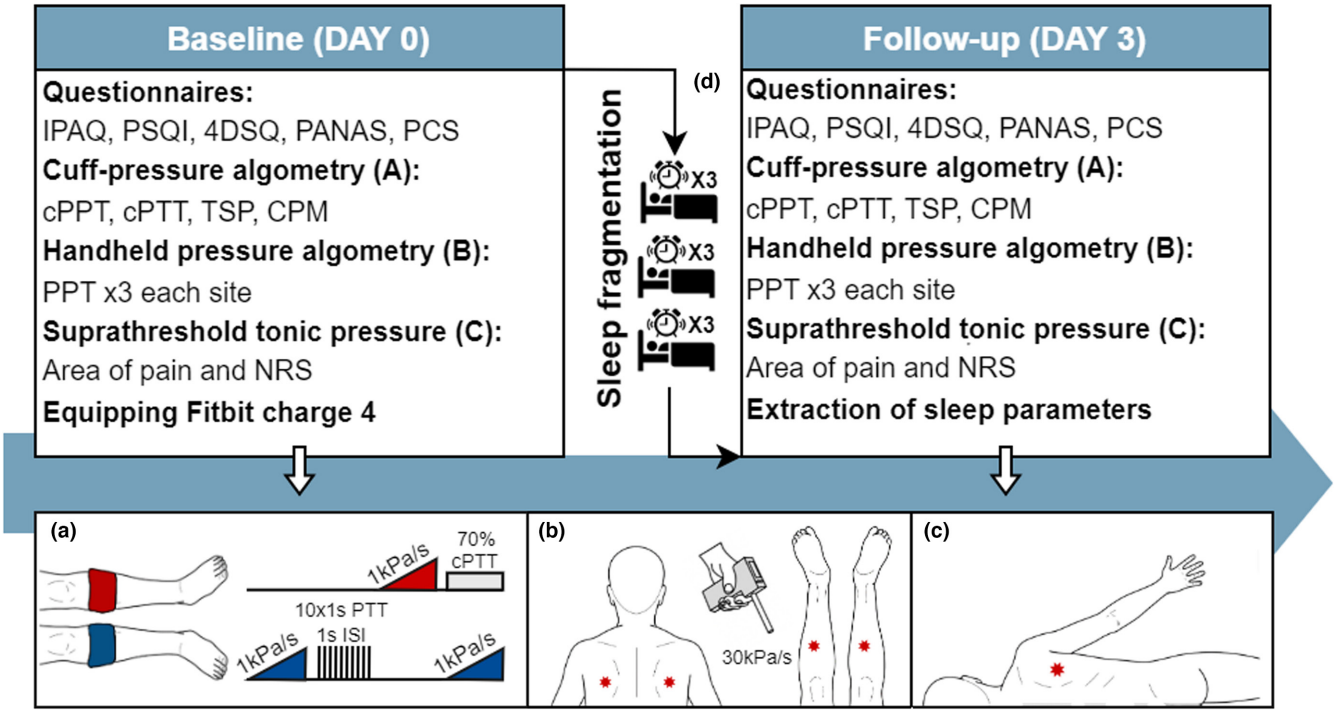

FIGURE 1 Overview of protocol showing timeline on baseline and follow-up, as well as the sleep disruption pattern. (a) cuff-pressure algometry; 1 and 3, ramped inflations of 1 kPa/s; 2, ten consecutive stimulations at an inflation rate of 100 kPa/s with 1-s inter-stimulation intervals; 4, a constant conditioning stimulation at 70% PTT and a ramped inflation of 1 kPa/s. (b) Handheld pressure algometry bilaterally at the infraspinatus and gastrocnemius muscles, three times at each site. (c) Suprathreshold tonic pressure at the dominant m. infraspinatus first for 5 s and then for 60 s. (d) Disrupted sleep pattern with three planned awakenings each night. IPAQ, International Physical activity questionnaire; PSQI, Pittsburgh sleep quality index; 4DSQ, The four-dimensional symptom questionnaire; PANAS, The positive and negative affective schedule; PCS, Pain catastrophizing scale; cPPT, cuff pressure pain threshold; cPTT, cuff-pressure tolerance threshold; TSP, temporal summation of pain; CPM, conditioned modulation of pain; PPT, pressure pain threshold; NRS, Numeric rating scale.

pulmonary, cardiac or chronic pain conditions as well as mental illness; recent or current acute pain; consumption of stimulants or painkillers on the mornings of the experiments; lack of ability to cooperate. Eligible participants were provided with written information about the study and signed informed consent. Participants were instructed to avoid the use of painkillers and stimulants during the study. The study was approved by the local Ethics committee (N-20180089) and conducted in accordance with the Helsinki Declaration.

2.2 | Questionnaires

Personal information was collected during the baseline session, including age, weight and height. Then a battery of the following validated questionnaires was administered.

The PSQI measures subjective sleep quality in one global score where higher scores indicate worse sleep quality (Buysse et al., 1989), and correlates with sleep diaries, insomnia diagnoses and depression scales, but not sleep actigraphy (Grandner et al., 2006). The short form of the IPAQ measures physical activity levels with higher scores denoting higher levels of physical activity. (Cleland et al., 2018; Hagstromer et al., 2006). The 4DSQ measures symptoms of somatization, anxiety, depression and distress experienced within the last week with higher scores indicating higher severity (Terluin et al., 2014). The PANAS measures positive and negative affect during the past week and higher scores on the positive scale reflect a high energy state with engagement, while higher scores on the negative scale reflect a state of lethargy (Watson et al., 1988). The PCS measures pain-related thoughts and feelings, where higher scores reflect a greater tendency to catastrophize about pain, which is correlated with more pain, negative pain-related thoughts and emotional distress (Sullivan et al., 1995).

2.3 | Wrist actigraphy

All participants wore a wrist activity tracker (Fitbit Charge 4, Fitbit Inc.) on their nondominant wrist from the end of the first session to the beginning of the second and were instructed to remove it only when showering. The device collects data and automatically transfers it via a dedicated smartphone application. Collected data included daily

physical activity level, sleep–wake stages and heart rate. The device tracks the total time spent asleep, time in bed and nightly awakenings. The Fitbit Charge 2 (the previous model of the Fitbit charge 4) has been reported to detect sleep–wake stages comparable to polysomnography (de Zambotti et al., 2018).

2.4 | Quantitative sensory testing

2.4.1 | Computer-controlled cuff-pressure algometry

A computer-controlled cuff-pressure algometer (Cortex Technology) attached to a pair of 13-cm tourniquet cuffs (VBM Medical) and an electronic visual analogue scale (eVAS; Cortex Technology, Aalborg University) was used for mechanistic pain profiling to investigate potential changes in peripheral and central pain sensitivity. The cuffs were positioned on the calves at the widest part, and the eVAS was anchored at 0 cm, with no pain, and 10 cm, the worst pain imaginable.

Cuff pain detection and tolerance thresholds

To determine the cPPT and cPTT a ramped test with a constant inflation rate of 1 kPa/s and a 100 kPa safety cut-off was used. This was performed first on the dominant and then the nondominant calf. The participants were instructed to start sliding the eVAS upward when the sensation first became painful, and to move it continuously, corresponding to their current pain throughout the ramp. They were instructed to press a stop button when they could not tolerate any further increases in pain. The cPPT was defined as the kPa pressure when the eVAS reached 1 cm on the dial. The cPTT was defined as the kPa pressure when the stop button was pressed, or the safety cut-off was reached. These definitions were based on previous studies using similar methods (Petersen, Olesen, et al., 2019; Staffe et al., 2019).

Temporal summation of pain

To investigate temporal summation of pain (TSP), ten repeated pressure stimulations were performed at the level of the cPTT previously recorded. Each stimulus had a duration of 1-s with 1-s interstimulus intervals. The participants were instructed to rate the pain intensity of the first stimulation on the eVAS and then adjust it for the subsequent stimulations, not returning it to zero between stimuli. The pain intensity rated on the eVAS was noted for each of the ten consecutive inflations. The degree of TSP was determined by subtracting the average of the first four inflations from the last three inflations (Petersen et al., 2016; Graven-Nielsen et al., 2015).

Conditioned modulation of pain

To investigate CPM a test stimulus and a conditioning stimulus were performed simultaneously. The test stimulus was a ramped inflation on the dominant calf with a constant inflation rate of 1 kPa/s and a 100 kPa safety cut-off. The conditioning stimulus was a tonic pressure on the nondominant calf at 70% of the cPTT previously recorded. The CPM effect was determined as the difference in cPPT before and during conditioning with a positive value denoting functional CPM.

2.4.2 | Manual pressure algometry

A handheld pressure algometer (Somedic) with a flat, 1-cm-diameter probe was used to obtain the PPTs. The pressure was applied at a constant rate of 30 kPa/s, perpendicular to the body surface. The PPT was defined as the point when the stimulation first was perceived as painful, indicated by the participant pressing a button. Assessment locations were bilaterally on the infraspinatus muscle (the equidistant point of the midpoint on the scapular spine, the inferior scapular angle and the midpoint on the medial scapular border) and gastrocnemius muscle (equidistant point of the popliteal line and the calcaneus). Each site was measured 3 times and separated by at least 60 s. The averaged PPTs for each site were used for analysis. The averaged PPT for the dominant infraspinatus muscle was used to calculate 120% PPTs for suprathreshold pain induction on the dominant shoulder.

2.4.3 | Suprathreshold pressure

To investigate sensitivity to suprathreshold pressure a tonic pressure of 120% PPT was applied to the dominant infraspinatus muscle (same position as defined for PPT). The pressure stimulation was performed twice; once for 5 s and once for 60 s respectively. The timeframes and intensity were chosen based on recommendations from previous studies (Arroyo-Fernandez et al., 2020; Doménech-García et al., 2016). Immediately following the pressure stimulation, the participant was asked to mark the area of the pain on a body chart and note the intensity of the pain on an NRS (0, no pain at all, and 10, the worst pain imaginable). The mean ratio of pixels marked on the picture was computed using the Pain Distribution software developed by Kanellopoulos et al. (Kanellopoulos et al., 2021).

2.5 | Experimental sleep disruption

The experimental sleep disruption protocol included three designated awakenings for three consecutive nights

to be conducted at home. The number of awakenings was chosen to mimic the average number of awakenings observed in patients with chronic pain with self-identified poor sleep, which is estimated to be 2.9 per night (Morin et al., 1998). The awakenings were scheduled at 00:00, 02:30 and 05:00 and were preplanned on the participant's smartphone as repeated alarms. The participant was instructed to complete a trivial task at each awakening: taking a picture of the FitBit watch face in front of their sink, with the lights turned on, and then forwarding the picture to the research team. Additionally, awakenings were confirmed with the picture and message, both showing the date and time.

2.5.1 | Sleep diary

The participants were instructed to make a sleep diary entry each morning during the study, covering various aspects related to their sleep: bedtime and hour of final awakening; whether they had difficulties falling asleep; how deep their sleep was; the number of awakenings, and their duration; sleep quality; level of rest. The subjective level of rest and quality of sleep were rated on a scale ranging from 0 to 100 with lower numbers reflecting less rest and lower quality of sleep. Depth of sleep was rated on a scale ranging from one; 'very deep' to five; 'very light'. The sleep diary had four intended entries, with the first at baseline and then for each of the three mornings after experimental sleep disruption.

2.6 | Statistical analysis

A power analysis was carried out to determine the required number of participants for the current study. An effect size of 0.5 was expected based on earlier findings of total sleep deprivation's effect on pain sensitivity (Staffe et al., 2019). A study with a power of 80% and a significant value of 0.05 should include at least 28 participants to demonstrate significant effects and, thus, 30 healthy participants were enrolled to account for potential dropouts.

All data are presented as means (±standard deviation, SD) unless otherwise stated. Paired samples t-tests were used to investigate changes in QST measures and questionnaire scores before and after experimental sleep disruption. Repeated-measures ANOVA was used to compare variables reported in the sleep diary over the three experimental nights and baseline. Likewise, repeated-measures ANOVA was used to investigate differences in wrist sleep actigraphy data for the three experimental nights. Assumptions were checked using appropriate statistical and visual methods, including normality, independence of observations and sphericity. When the sphericity assumption was not met, Greenhouse–Geisser correction was used. Statistical analyses were performed in SPSS Statistics (IBM SPSS Statistics for Windows, Version 27.0) with an accepted significance level of $p < 0.05$.

3 | RESULTS

3.1 | Participant characteristics

Thirty participants were recruited. Participants had a mean age of 24.6 ± 3.1 years and a mean BMI of 23.5 ± 3.0 kg/m^2. All participants completed both sessions and were included in the data analysis. Eight participants were tested for pain sensitivity before noon, while the remaining were tested in the afternoon. The participants were always tested at the same time of day before and after the sleep disruption to mitigate the effects of circadian rhythmicity on pain sensitivity (Daguet et al., 2022). Furthermore, 13 participants were scheduled over a weekend, while the rest were scheduled during the weekdays. Four participants missed one of the nine scheduled awakenings (two missed the 03:00 awakening and two missed the 05:00 awakening), whereas two woke up within 45 min of the planned awakening and documented it by completing the task. A responder versus nonresponder analysis were carried out to investigate whether those who missed an awakening were less affected by the sleep disruptions. The analysis revealed no significant differences in all other measured sleep variables between those with full compliance and the four who missed one awakening, suggesting that the four participants were equally as impacted as those who completed all awakenings.

3.2 | Induced sleep disruption for three nights

Participants reported an average of 3.2 ± 1.1 awakenings and 28.2 ± 28.3 min of awake time per experimental night in the sleep diary, whereas the wrist actigraphy suggested an average awake time per night of 1 h and 12.4 ± 14.8 min and a total sleep time of 7 h and 23.5 (±54.7) min. The sleep quality reported in the sleep diary was significantly different over baseline and the three experimental nights ($F_{(2.3,\ 66.6)} = 14.61$, $p = 0.000$, Figure 2) and Bonferroni corrected post hoc showed that sleep quality was significantly lower at experimental night one ($p < 0.001$), two ($p = 0.002$) and three ($p = 0.009$) compared to baseline. Additionally, the sleep quality of the second experimental night was rated significantly higher

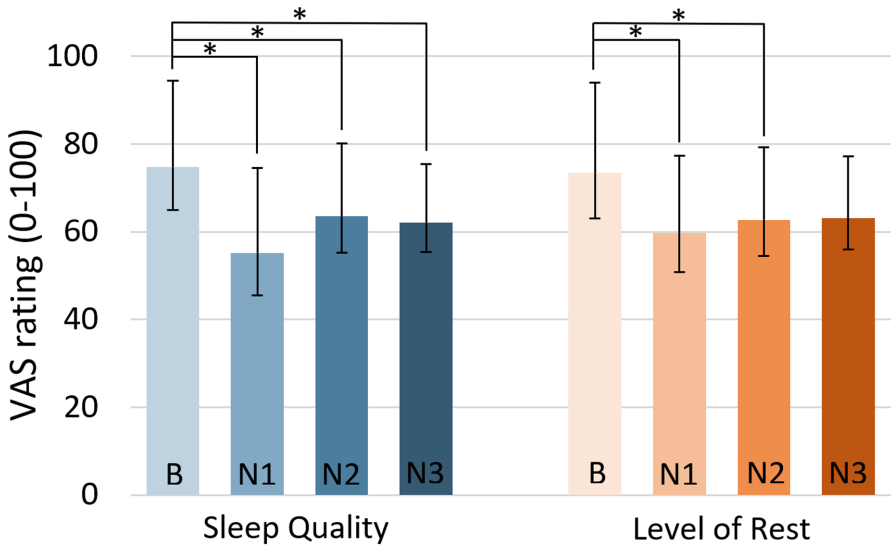

FIGURE 2 Mean level of rest and mean sleep quality rated on a scale from 0 to 100 (0; worst sleep quality imaginable/lowest level of rest imaginable and 100; best sleep quality imaginable/highest level of rest imaginable) in the sleep diary by the participants presented for each of the three experimental nights and baseline. Sleep quality ($F_{(2.3, 66.6)} = 14.61$, $p = 0.000$) and level of rest ($F_{(2.4, 68.8)} = 6.76$, p = 0.001) were significantly different over baseline and the three experimental nights. Mean ± SD; *, $p < 0.05$. B, Baseline; N1, Experimental night 1; N2, Experimental night 2; N3, Experimental night 3.

TABLE 1 Overview of data from wrist actigraphy. Shown for each of the three experimental night (N1, N2, N3) and averaged (avg.). Data are presented as minutes (min) with standard deviations (SD).

WRIST ACTIGRAPHY	N1	N2	N3	Avg.
Total sleep, min (±SD)	454 (±80)	446 (±120)	430 (±71)	443 (±92)
Awakenings, min (±SD)	72 (±18)	75 (±27)	71 (±23)	72 (±23)
Time in bed, min (±SD)	526 (±93)	521 (±140)	501 (±88)	516 (±109)

than the first ($p = 0.002$). The difference in ratings of level of rest was also significantly different over the four nights ($F_{(2.4, 68.8)} = 6.76$, $p = 0.001$, Figure 2) and Bonferroni corrected post hoc showed that the first ($p = 0.001$) and second ($p = 0.01$) experimental nights were rated significantly lower than the baseline night. No significant differences were found between the three experimental nights for any of the sleep parameters measured by wrist actigraphy, which can be seen in Table 1.

3.3 | Changes in questionnaire scores

Participants scored significantly lower positive PANAS ($t_{29} = -2.21$, $p = 0.035$) after sleep disruption. No other questionnaire scores were significantly changed after sleep disruption.

3.4 | Effects of disrupted sleep on pain sensitivity

Lower cPTT was found at follow-up compared with baseline ($t_{29} = 2.3$, p = 0.028, Figure 3c) but there were no significant changes in cPPT. Furthermore, significant reductions were found in PPTs over all 4 points measured: the dominant calf ($t_{29} = 3.4$, $p = 0.002$, Figure 4), the nondominant calf ($t_{29} = 3.5$, $p = 0.001$, Figure 4), the dominant shoulder ($t_{29} = 3.5$, $p = 0.001$, Figure 4) and the nondominant shoulder ($t_{29} = 3.3$, $p = 0.003$, Figure 4) when comparing baseline to follow-up.

3.5 | Effects of disrupted sleep on measures of central pain sensitization

TSP was significantly facilitated at follow-up compared to baseline ($t_{29} = -2.4$, $p = 0.022$, Figure 3a). No significant differences were found in CPM when comparing baseline (10.6 ± 14.4) to follow-up (11.7 ± 13.7; $t_{29} = -0.54$, $p = 0.59$, Figure 3b).

3.6 | Sensitivity to suprathreshold pressure

NRS ratings for 5 s of suprathreshold pressure were significantly increased at follow-up compared to baseline

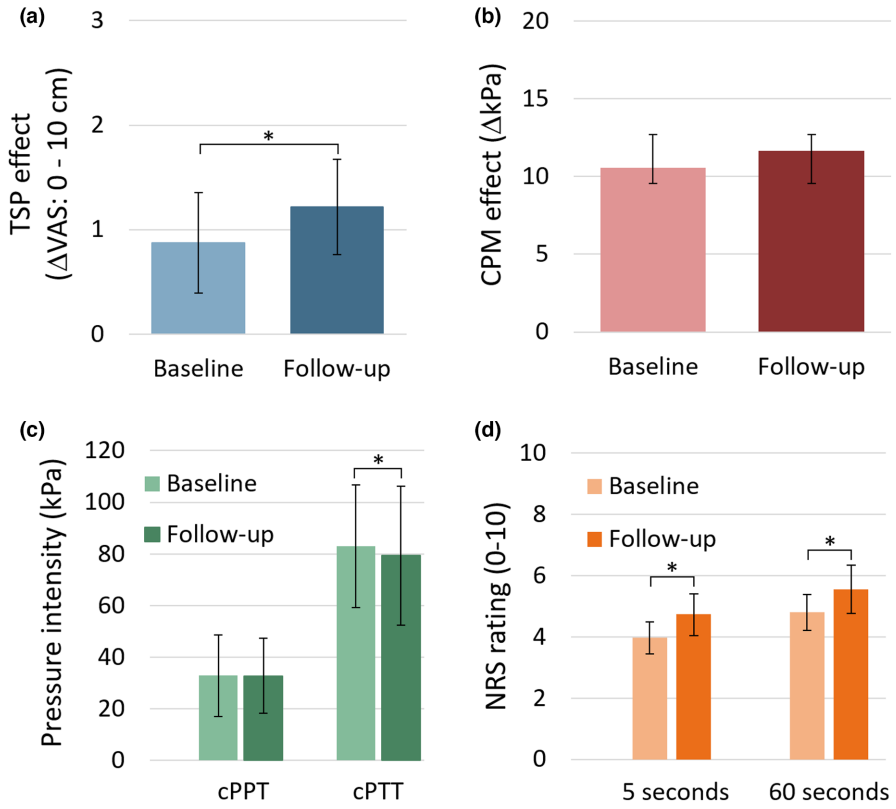

FIGURE 3 (a) Temporal summation of pain as VAS difference between the first 4 and last 3 ratings. Shown before (baseline) and after sleep disruption (follow-up, $t_{29} = -2.4$, $p = 0.022$). (b) CPM effect as difference in cPDT with and without conditioning. (c) Cuff pressure pain thresholds (cPPT) and cuff pain tolerance thresholds (PTT) before sleep disruption (baseline) and after sleep disruption (follow-up) only shown for the nondominant calf. The cPTT was significantly lower after sleep disruption ($t_{29} = 2.3$, $p = 0.028$). (d) Ratings of pain intensity on a numeric rating scale (NRS; 0–10) during suprathreshold pressure application for 5 and 60 s. NRS was significantly lower after sleep disruption (follow-up) for both 5 ($t_{29} = 3.6$, $p = 0.001$) and 60 s ($t_{29} = 2.1$, $p = 0.044$) of pressure compared to baseline. Mean ± SD; *$p < 0.05$.

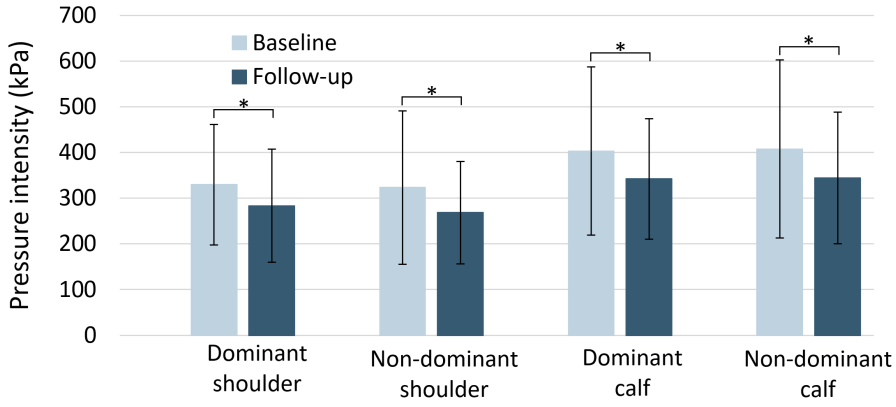

FIGURE 4 Pressure pain thresholds (PPTs) measured with handheld pressure algometry before sleep disruption (baseline) and after sleep disruption (follow-up) measured bilaterally on the shoulders (infraspinatus muscle) and calves (gastrocnemius muscle). The PPTs were significantly lower after sleep disruption for the dominant ($t_{29} = 3.5$, $p = 0.001$) and nondominant shoulder ($t_{29} = 3.5$, $p = 0.001$) as well as the dominant ($t_{29} = 3.4$, $p = 0.002$) and nondominant calf ($t_{29} = 3.5$, $p = 0.001$). Mean ± SD; *$p < 0.05$.

($t_{29} = 3.6$, $p = 0.001$, Figure 3d). Likewise, NRS ratings for 60 s of suprathreshold pressure were significantly increased at follow-up compared to baseline ($t_{29} = 2.1$, $p = 0.044$, Figure 3d). Additionally, the area marked as painful on a body chart after 60 s of suprathreshold pressure was significantly larger after the sleep disruption

($t_{29} = -3.1$, $p = 0.005$, Figure 5) with a mean picture ratio of 0.76 (±0.57) compared to baseline with a mean picture ratio of 0.49 (±0.38).

4 | DISCUSSION

This study demonstrated that sleep disruption for three consecutive nights induced hypersensitivity to pain, facilitated temporal summation of pain and lowered positive affect when compared to baseline parameters.

4.1 | Experimental sleep disruption

Sleep disturbances are known to predict next-day pain, while current pain can predict sleep duration, indicating a bidirectional relationship (Edwards et al., 2008). Sleep disruptions are previously used to investigate measures of peripheral (Iacovides et al., 2017; Schuh-Hofer et al., 2013; Simpson et al., 2018; Staffe et al., 2019) and central (Smith et al., 2019; Staffe et al., 2019) sensitization. The sleep disruption protocol developed by Smith et al (Smith et al., 2007) was found to impair endogenous inhibition of pain and increase spontaneous pain, and variations have since been used to investigate sleep continuity disturbances' effect on pain sensitivity (Iacovides et al., 2017; Smith et al., 2019). The current sleep disruption protocol was designed purely to disturb sleep continuity, mimicking the average number of nightly awakenings seen in patients with chronic pain (Morin et al., 1998) with no restriction of total sleep time. There were a few discrepancies between paper sleep diaries and actigraphy regarding sleep parameters, such as time spent awake, which is consistent with literature (Jungquist et al., 2015; Moore et al., 2015). Thus, the average total sleep time of 7.4 h was slightly longer sleep than reported by most patients with chronic pain (Keilani et al., 2018) and longer than the maximum 280 min in the previously discussed sleep disruption protocol (Iacovides et al., 2017; Smith et al., 2007, 2019). However, the participants' subjective quality of sleep as well as their perceived level of rest was successfully and significantly lowered, similar to previous sleep disruption protocols (Iacovides et al., 2017; Rosseland et al., 2018; Smith et al., 2019) and sleepiness in healthy subjects have previously been linked to hyperalgesia (Chhangani et al., 2009).

Notably, the subjective sleep quality was most affected by the sleep disruptions on after the first experimental night, whereas the following nights were rated with significantly higher sleep quality scores and after the third night the level of rest was not significantly different from baseline. This could be due to a possible habituation, which has also been reported for subjective sleep quality (Elmenhorst et al., 2008), sleepiness (van Dongen et al., 2003) and alertness (Drake et al., 2001) after sleep

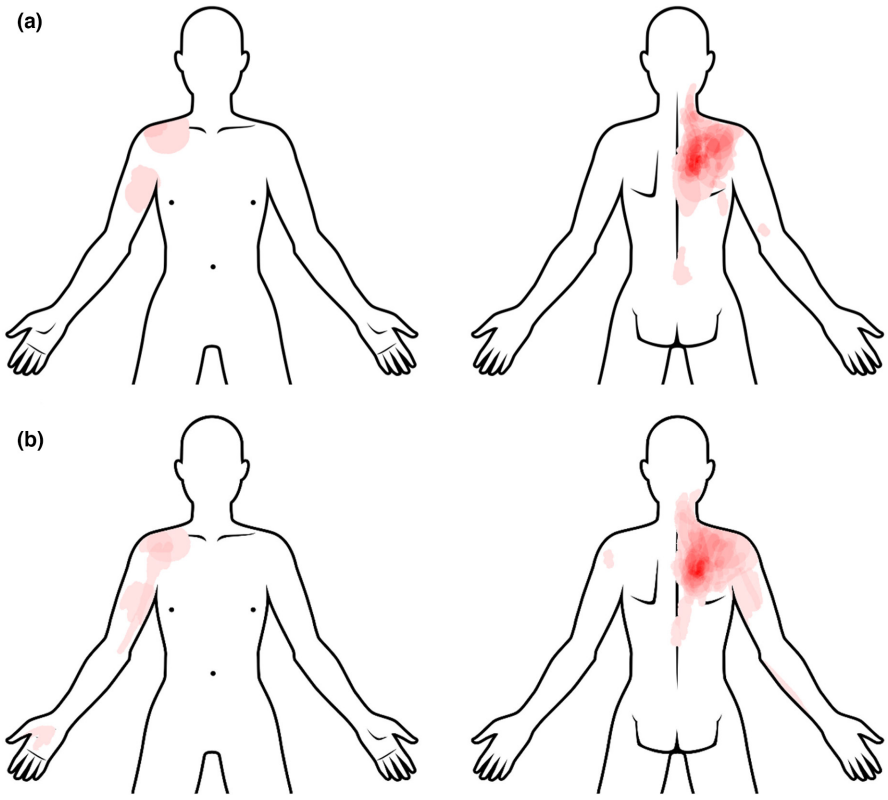

FIGURE 5 Body chart showing an overlay of the area of pain marked by the 30 subjects after application of 60 s of suprathreshold pressure at (a) baseline and (b) follow-up. A more saturated red colour represents an area more frequently marked. The pressure was always applied on the dominant shoulder, but the image was mirrored for all with left-hand dominance. The marked area was significantly larger at follow-up with a mean picture ratio of 0.76 compared to 0.49 at baseline ($t_{29} = -3.1$, $p = 0.005$).

restriction. This possible habituation effect in subjective ratings happened, even though cognitive performance measures were consistently lowered, leading to the hypothesis that subjects cannot reliably evaluate the impact of chronic sleep loss (van Dongen et al., 2003).

4.2 | The effect of sleep disruption on affective state

Several psychological factors have been identified as potential mediators of the sleep and pain relationship including mood, depression, anxiety and stress (Whibley et al., 2019). The current study found lowered positive affect after sleep disruption, which is consistent with literature, where positive affect has been found lowered after both total (Talbot et al., 2010) and partial sleep deprivation (Finan et al., 2017), while negative affect remains unaltered (Finan et al., 2017; Talbot et al., 2010). One study found the effect of partial sleep deprivation on mood to be mediated by decreased amounts of deep sleep with the greatest effect of disrupted sleep compared to restricted sleep (Finan et al., 2017), while another study did not find mood to be significant in the sleep–pain interaction (Rosseland et al., 2018). Moreover, patients with chronic pain with poor sleep report higher levels of anxiety and depression as well as higher pain intensities (Larsen et al., 2021). Evidently, it seems like sufficient sleep is crucial for cognitive functions such as emotion regulation (Huber et al., 2022; Walker, 2009), which might explain the decrease in positive affect observed in the current study.

4.3 | Sleep disruption and measures of central pain sensitization

The wind-up process of dorsal horn neurons can be quantified in humans using TSP (Latremoliere & Woolf, 2009), and is considered consequential to a progressive increase in the magnitude of responses to consecutive nociceptive stimuli (Mendell, 2022). The current study found increased facilitation of TSP following sleep disruption, which is consistent with previous reports after total sleep deprivation (Staffe et al., 2019), forced awakenings for two nights (Smith et al., 2019), and restricted sleep (Simpson et al., 2018). However, there are also reports of no observed changes in TSP after total sleep deprivation (Schuh-Hofer et al., 2013). The discrepancies might be attributed to methodological differences, as the discussed studies used varying types of both sleep interventions and modalities of noxious stimulations to induce TSP (Horn-Hofmann et al., 2018). Facilitated TSP is also frequently observed in patients with chronic pain (O'Brien et al., 2018) and is believed to reflect a more pronociceptive pain phenotype (Yarnitsky et al., 2014). The current results suggest that even modest disruptions of sleep continuity for three consecutive days can adversely impact facilitatory central pain mechanisms.

The current study did not find any significant differences in CPM following sleep disruption. Previous reports of changes in CPM after sleep disruption have been inconsistent with findings of it being both impaired (Eichhorn et al., 2018; Smith et al., 2007; Staffe et al., 2019), stronger (Matre et al., 2016), and not changed (Rosseland et al., 2018; Smith et al., 2007). Other studies suggest that the effect of sleep deprivation on endogenous modulation of pain might be sex-dependent and specifically seen in females (Eichhorn et al., 2018). However, the results might be influenced by the type of sleep interventions; one study comparing total sleep deprivation to sleep disruption found that only sleep continuity disturbance had a significant effect on pain inhibition, however, total sleep time was restricted to 280 min (Smith et al., 2007). Furthermore, a recent study found no relationship between CPM and sleep disturbances or pain intensity in a population of patients with chronic pain (Song et al., 2022). The unaltered CPM in the current study might be attributed to the degree of sleep disruption, which was solely based on sleep continuity disturbance, while the studies observing impaired CPM used some form of total sleep deprivation (Eichhorn et al., 2018; Smith et al., 2007; Staffe et al., 2019) or restricted total sleep times (Smith et al., 2007).

4.4 | Sleep disruption and pain sensitivity

The current study found hypersensitivity to pain following sleep disruption. Both total sleep deprivation and sleep disruption have previously been shown to cause increases in sensitivity to various test modalities in healthy subjects (Eichhorn et al., 2018; Iacovides et al., 2017; Onen et al., 2001; Rosseland et al., 2018; Schuh-Hofer et al., 2013; Smith et al., 2007, 2019; Staffe et al., 2019), and patients with chronic pain are known to have significantly decreased PPTs compared to healthy controls (Amiri et al., 2021). This apparent hyperalgesic effect of sleep disruptions might be partly attributed to a rise in prostaglandins, which has previously been observed in healthy individuals after total sleep deprivation (Onen et al., 2001) and can sensitize peripheral nociceptors, as well as mediate pain processing at a spinal level (Ito et al., 2001; Taiwo & Levine, 1988). Furthermore, prostaglandins are involved in sleep homeostasis, and their inhibition has been shown to disrupt sleep continuity and decrease

the amount of deep sleep (Horne et al., 1980; Murphy et al., 1994), which might contribute to the vicious loop of chronic pain and poor quality of sleep. Finally, interleukin 6 (IL-6) is upregulated in patients with poor quality of sleep (Irwin et al., 2016), and IL-6 is known to sensitize the nervous system (Schaible, 2014), which can be measured as localized or widespread pressure hyperalgesia. Another possible mechanism for increased pain sensitivity following sleep disruptions might be a cortical amplification of nociceptive signals (Tiede et al., 2010).

The current study also found increased sensitivity to suprathreshold pressure following sleep disruption. Suprathreshold pressure sensitivity is thought to be driven by both peripheral and central mechanisms (Doménech-García et al., 2016; Laursen et al., 1999). Sensitivity to 10 s of suprathreshold pressure has previously been found to increase after sleep restriction, but not after habitual sleep, confirming the mediating effect of sleep insufficiency (Ødegård et al., 2015). However, another study investigating suprathreshold pain in migraineurs and healthy controls found no changes in suprathreshold pain sensitivity after sleep restriction for either group (Neverdahl et al., 2022). Expansion of the painful area during 60 s of suprathreshold pressure was also observed following sleep disruption in the current study, following earlier observations of pain referral from the infraspinatus muscle with painful areas extending beyond the origin of the noxious stimulation (Arroyo-Fernandez et al., 2020). Expansion of pain areas is often observed in patients with chronic pain and is thought to be caused by convergence of adjacent receptive fields of dorsal horn neurons, which is believed to be a characterizing feature of dorsal horn windup (Graven-Nielsen & Arendt-Nielsen, 2010). The current result supports the notion that sleep continuity disturbance affects measures of central pain sensitization, and perhaps specifically facilitatory mechanisms, indicated by increased sensitivity to both prolonged suprathreshold pressure and repeated pressure stimulations.

4.5 | Limitations

The current study did not include a control group, hence controlling for any potential habituation to the pain sensitivity tests was not possible, and thus the results should be interpreted with caution. The current study relied on self-reported assessment of sleep time and assessment using the FitBit device, which could limit the results, and this should be considered when interpreting the results of the study. The FitBit Charge 4 is used in the current study to measure sleep–wake stages at the participants' home. However, the accuracy and reliability of the device have yet to be investigated in, for example, an at home setting (De Zambotti et al., 2018). Although no baseline night with actigraphy was conducted, subjects reported baseline sleep in the form of both a sleep diary entry and PSQI, which were used to assess the difference in sleep quality between baseline and the experimental nights. The four subjects who missed an awakening were all included in the analysis, as wrist actigraphy showed that their sleep was equally, or more impacted than those who had full compliance. However, some responder versus nonresponder differences might not be detectable with the sleep data measured in the current study.

5 | CONCLUSION

The current study successfully implemented a three-night sleep disruption protocol in 30 healthy subjects. Sleep disruption induced increased sensitivity to several measures of central pain sensitization with hypersensitivity to pain, expanded pain areas and facilitated temporal summation of pain. The results emphasize the importance of studying the effect of poor sleep on pain and future studies should further investigate these relationships in patients with chronic pain.

CONFLICT OF INTEREST STATEMENT

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