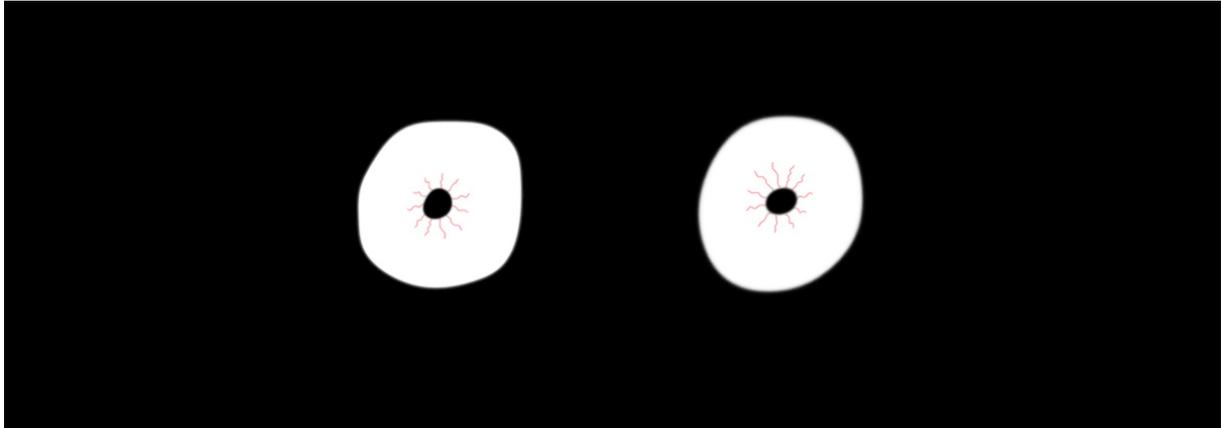


# The effect of sleep deprivation on pain perception

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## Abstract

Sleep disturbances have been associated with (chronic) pain. Within this subject, a theory linking sleep deprivation to a change in pain perception is becoming increasingly popular. Studies performed to supply this hypothesis with evidence, are mostly clinical studies. In these studies, patients with a disease (e.g. fibromyalgia) characterized by chronic pain and insomnia were sleep deprived after which their pain threshold was measured. Most results indicated a significant increase in pain perception of these patients. Interestingly, the healthy control group used in the studies mentioned above, showed fibromyalgia-like symptoms after being sleep deprived. Furthermore, after sleep recovery or using hypnotics, these symptoms disappeared in fibromyalgia patients as well as in the control groups. In this review, these findings are further explored by evaluating different experimental studies on the effects of sleep deprivation on pain perception in animals and humans. Also, the potential physiological and neurological mechanisms through which sleep deprivation may affect pain perception will be discussed. All pathways (opioidergic, serotonergic, norepinephrine and GABAergic) discussed in this review showed a change in neurotransmitter or mechanism of action after sleep deprivation in the subjects, that eventually may result in a higher pain perception. The results imply that sleep deprivation leads to a higher pain perception. Nevertheless, the mechanism of action through which sleep deprivation influences pain perception is not yet fully known. Even though there are several studies on the effect of sleep deprivation on pain perception, no firm conclusions can be made.

## Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
CNS	central nervous system
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
GABA	$\gamma$ -aminobutyric acid
GHB	$\gamma$ -hydroxybutyrate
HPA	hypothalamic-pituitary-adrenal axis
IASP	International Association for the Study of Pain
NREM	non-rapid eye movement
PAG	periaqueductal grey
REM	rapid eye movement
RVM	rostral ventromedial medulla
SWS	slow-wave sleep

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## 1 Introduction

Pain is described as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” according to the International Association for the Study of Pain (IASP). Pain typically involves noxious stimuli or events that activate nociceptors in the body’s tissues that transmit signals to the central nervous system (CNS), where they are processed and generate multiple responses, including the “unpleasant sensory and emotional experience”.

Noxious stimuli are events that damage or threaten to damage tissue. Every tissue has different stimuli that can activate particular nociceptors (receptor types at the unmyelinated nerve endings, specialized in determining (potentially) damaging stimuli). Thus, pain is the feeling (perception) of irritating, sore, stinging, aching, throbbing, miserable, or unbearable sensations arising from a part of the body. Nociception is the sensory process that provides the signals that trigger pain [1,2].

For a longer period of time, a relation between sleep and pain is investigated. Mostly in human studies, where sleep disruption and pain in depressed or diseased persons was compared to healthy control groups, but also in animal studies. It becomes increasingly convincing that sleep and pain are connected, but more research is needed to be able to apply these findings clinically. For the purpose of clarifying the studies that have been done and conclusions that have been made, this research review was written. The central question in this review will be whether or not sleep deprivation influences pain perception and what the underlying mechanisms of action may be.

Firstly, in the second paragraph of this review, the relationship between sleep and pain is described by comparing clinical studies about fibromyalgia, where sleep deprivation may be either a cause or consequence of this chronic disease. Numerous studies were performed on the relationship of sleep and pain using fibromyalgia as base, which is why in this report this disease was chosen as an introduction to sleep and pain. Secondly, animal and human experimental studies are described to give insight in for example how pain is measured. In this section, the focus will be on the effect of sleep deprivation on pain perception. Following, a more extensive picture of the different – most important – mechanisms of action of pain is given in the fourth paragraph, and finally, in the last paragraph, the outcomes of this review are discussed.

## 2 Clinical relationship sleep and pain

The majority of studies performed to investigate the relationship between sleep and pain used fibromyalgia patients as subjects and this disorder may shed light on the relationship between sleep disruption and pain. With a prevalence of 2% worldwide, fibromyalgia is characterized by chronic widespread musculoskeletal pain. Additional symptoms are, among others: non-refreshing sleep, insomnia, fatigue, functional impairment, cognitive dysfunction, and depression [3,4].

Fibromyalgia is also characterized by severe sleep problems. The activity of the brain (also during sleep) can be measured by electroencephalography (EEG). This technique is among other purposes used to characterize these sleep problems. EEG rhythms often correlate with states of behavior. The EEG rhythms are categorized by their frequency range. The alpha

rhythms (8-13 Hz) are associated with quiet, waking states [5]. In several studies [6,7], an increased frequency of alpha waves was observed in fibromyalgia patients during non-rapid eye movement (NREM) sleep. NREM sleep is divided into the following stages: 1) light, 2) intermediate, 3,4) slow-wave sleep (SWS). SWS is thought to be important for restoring the ability of the body to function. Sleep was measured by polysomnography recordings and scoring of the sleep was done visually by Rechtschaffen and Kales criteria (1968). Furthermore, the pressure pain thresholds (minimum force applied that induces pain [8]) decreased overnight. Another study [9] also proved fibromyalgia patients experience more arousal episodes (increases of brain activity) during night sleep compared to healthy control subjects. This study, however, noticed these increased arousal episodes were strongly related to respiratory abnormalities, other consequences fibromyalgia patients have to deal with [10].

## 2.1 Healthy subjects and fibromyalgia

As mentioned above, sleep disruption and insomnia are symptoms of fibromyalgia. In a study, [11] healthy subjects were sleep deprived. Fascinatingly, these healthy subjects showed fibromyalgia-like musculoskeletal symptoms, an increase in muscle tenderness, and a reduced pressure pain threshold after their SWS was selectively deprived. SWS was identified as delta EEG waves with frequencies of 0.5-2 Hz. REM sleep was identified when rapid eye movements occurred and low amplitude EEG was observed. In this study, a control group was missing, thus the observed results might be disputed. Though, other studies [12,13] confirm the previously described findings [11]. In these studies, recovery by increasing the SWS to the normal level reduced muscle tenderness and normalized the pain threshold in the healthy subjects showing fibromyalgia-like symptoms after being SWS deprived. The amount of REM sleep and normalized mechanical pain tolerance scores were not significantly correlated. Polysomnographic recordings were used to observe subjects' sleep. SWS was scored visually according to the Rechtschaffen and Kales criteria (1968). Criteria for REM sleep were the occurrence of rapid eye movements, and other properties typical for this sleep. Both types of sleep were interrupted by an auditory stimulus (calling subject's name), or by physical stimulation (shaking) when required. Pain was measured by applying thermal and pressure pain, both by using dolorimeters. A dolorimeter is an instrument that is used to measure pain thresholds and tolerance. It has a tension scale reaching from zero to ten, zero being no tension, and ten being the maximal force applied to a joint, comparable with the force of pressing a thumb on the subject's joint. This will not cause tenderness in normal joints but may cause tenderness in persons with a lower pain threshold. The investigator applies the rubber tip of the instrument and the chosen force (zero to ten) on the subject. The subject then indicates the pain this force causes [14]. REM sleep and SWS reduction were observed in parallel with a decreased pain threshold and an increase in muscle tenderness. A bidirectional relationship between sleep and pain is supported by these data, that can be seen in figure 1. This figure visualizes pain (and some underlying causes) that may lead to poor sleep quality and poor sleep quality in turn may lead to stress and conditions of pain.

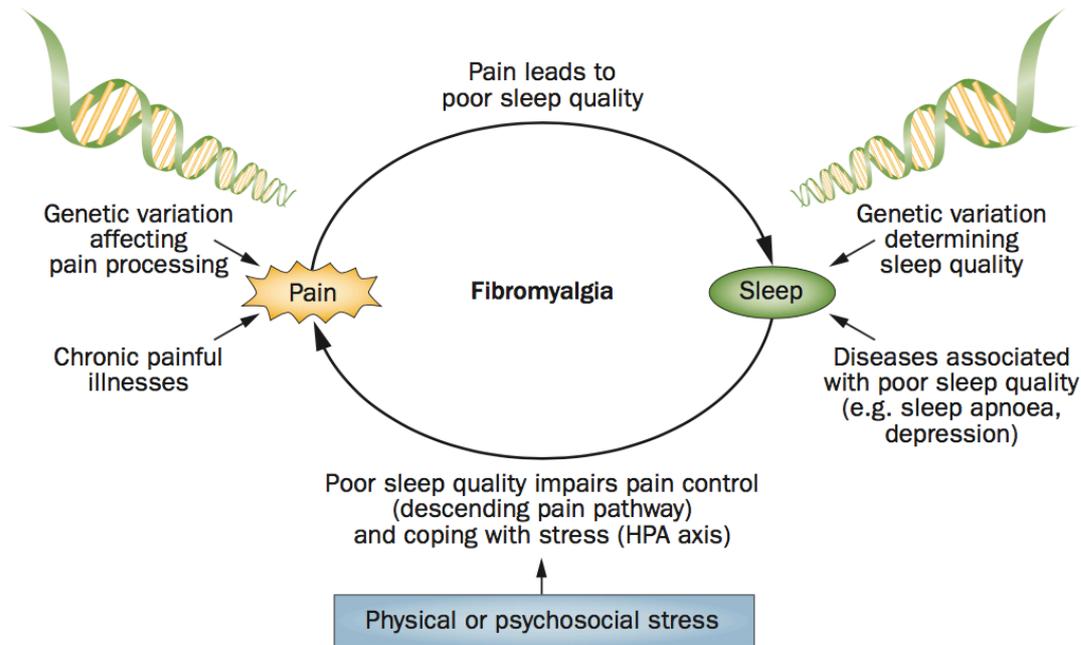


Figure 1. Bidirectional relationship between pain and sleep. HPA = hypothalamic-pituitary-adrenal axis [4].

## 2.2 Treatment

Treatment of fibromyalgia is mainly focusing on decreasing pain and increasing restorative sleep. Pharmacologic treatments include analgesic and/or sedative-hypnotic agents to address the pain and insomnia. Pregabalin is a medicine that reduces pain and improves sleep [15] and is so far the only used treatment for fibromyalgia. The effect of pregabalin on polysomnographic measures of sleep and pain in fibromyalgia was assessed in several studies. Here, a randomized, placebo-controlled study [16] will be outlined. The polysomnographic recording and scoring of the sleep were carried out using the Rechtschaffen and Kales manual (1968). Patients participating in the study completed a daily diary about sleep (number of awakenings), and rated tiredness in the past 24 hours, pain, and the quality of their sleep on a scale from zero to ten.

Another drug that may have positive effects on pain by promoting sleep is sodium oxybate. Sodium oxybate is the sodium salt of  $\gamma$ -hydroxybutyrate (GHB). Patients that have difficulties in regulating their wake-sleep cycle, have a disease called narcolepsy and are treated with this medicine. Sodium oxybate is a  $\gamma$ -aminobutyric acid (GABA) receptor agonist and has been shown to increase the SWS, and to decrease the number of arousal periods [17]. Some narcolepsy patients also show fibromyalgia symptoms. Treating these patients with sodium oxybate showed improvement of both their fibromyalgia and narcolepsy symptoms. In placebo-controlled trials [18-20], fibromyalgia patients were given sodium oxybate, which significantly increased total sleep time, enhanced slow-wave sleep, reduced alpha waves, and reduced the number of arousal episodes. Importantly, sodium oxybate also decreased the severity of pain and the tender point index of these patients. The tender point index was used to evaluate 18 selected pressure points used in the diagnosis of fibromyalgia. Besides using the tender point index and polysomnography, patients kept a diary in which they daily described what kind of pain they felt. The GABAergic pathway that this drug affects will be further explained in paragraph 4.4.

### 3 Experimental evidence

In order to get a better understanding of how sleep and pain are connected, animal and human studies are described in this section. The aim of this section is to prove that sleep deprivation leads to a change in the perception of pain.

#### 3.1 Animal experiments

An animal study [21] tested the effect of REM sleep deprivation and sleep recovery on the vocalization threshold in rats exposed to a mechanical noxious stimulus. REM sleep was deprived performing the 'inverted flower pot' technique. Using this technique, the rats were housed on top of platforms surrounded by water. When losing muscle tone, the rats fell into the water, and awakened. Control rats were housed in tanks filled with water with large platforms, permitting the animals a total relaxation and REM sleep. The Randall-Selitto paw pressure test was performed by applying increasing pressure to the hind paw of the rat, until it withdrew its paw or showed more complex behavior, such as escaping or vocalization. Nociceptive thresholds for the appearance of a given behavior, vocalization in this study, was then measured [22]. The results showed that a REM sleep deprivation of 48 and 72 hours significantly reduced the vocalization thresholds to mechanical noxious stimuli. During the recovery period, the vocalization threshold returned very rapidly to the baseline level. Another experiment used in a similar study [23] to assess nociception is the tail electric shock test.

#### 3.2 Human experiments

Utilizing animals to study the relationship between sleep and pain gives lots of opportunities, such as: making knockout models, manufacture lesions in particular parts of the brain, or perform experiments that would not be ethical for humans. Yet, mimicking human diseases or syndromes that are not fully understood is almost impossible. A disease like fibromyalgia is very complex, and a perfectly simulated animal model has up until now not been accomplished. Of course, investigating the relation between sleep deprivation and pain is also done utilizing healthy animal models and human subjects, but, for example, treatment of a disease may give rise to new research questions. For this reason, human studies may contribute as much as animal studies do to the evidence of the bidirectional relationship between sleep and pain.

In the following study, described in Lautenbacher's review [3], the authors concluded that disrupting SWS for several nights is associated with, among others, a decreased pain threshold. In this study, SWS was deprived by detecting delta waves (indicative of SWS) on EEG, measuring brain activity during sleep. A tone was delivered until delta waves disappeared. Pain was quantified by measuring the musculoskeletal tender points using a dolorimeter, skinfold tenderness by the skin roll procedure, and subjects completed questionnaires on bodily feelings, symptoms, and mood. Pain intensity was measured by a visual analog scale. This scale ranges from zero, identified as "no pain", to 100 (100-mm scale), identified as "worst imaginable pain". Thus, the higher the score, the greater the pain intensity. This scale was obtained from postsurgical patients who described their pain intensity as none, mild, moderate, or severe. There are no normative values available [24].

**Box 1 | Pain pathway**

Most studies that report a relationship between sleep deprivation and pain perception are descriptive and do not include a deeper insight into the mechanism of action of pain related to sleep deprivation or sleep in general.

Noxious stimuli make the nociceptor membranes stretch or bend, and activate ion channels that cause the cell to depolarize and generate action potentials. Another way to activate an action potential is by releasing a number of substances that also cause ion channels to open. Responses to the noxious stimulation triggers are, among others, the unpleasant emotional state of pain, withdrawal reflexes, and an increase in the heart rate and blood pressure. Some nociceptive responses do not necessarily indicate pain. The transduction of painful stimuli occurs in the nerve endings of unmyelinated C fibers and lightly myelinated A $\delta$  fibers.

Nociceptors conduct the electrical signaling message to the dorsal horn of the spinal cord. Information continues to the brainstem and ultimately in the cerebral cortex where the perception of pain is generated. There is not a single pathway that is responsible for the generation of pain in the CNS, but a combination of pathways is involved in the propagation of signals to the cerebral cortex. The perception of pain results from processing of the electrical signals in various regions of the brain. This explains the varied responses and emotional reactions when an individual experiences pain [1,2]. The above explained mechanism of pain perception is illustrated in figure A.

Figure A. Pain mechanism and its pathway.

Source: Häuser, W., Ablin, J., Fitzcharles, M.-A., Littlejohn, G., Luciano, J. V., Usui, C., & Walitt, B. (2015). Fibromyalgia. *Nature Reviews Disease Primers*, (August), 15022.

The mechanisms by which sleep deprivation and recovery modifies pain thresholds is not fully understood. Some data demonstrates that opioidergic, serotonergic, noradrenergic and GABAergic pathways involved in pain are also influenced by sleep manipulations. These mechanisms are briefly highlighted in paragraph 4 [3].

In 2000, a study [12] in which the effects of total sleep deprivation, REM sleep and SWS interruption and sleep recovery on mechanical and thermal pain sensitivity in healthy adults were compared was published. The investigators found that REM sleep and SWS interruption both decreased mechanical pain thresholds. SWS was recorded and scored by detecting delta waves as explained before. According to these observations, selective SWS disruption could be performed. Subjects undergoing total sleep deprivation were not allowed to sleep for the whole night. Tolerance thresholds to mechanical and thermal pain were assessed using an electronic pressure dolorimeter (dolorimeter that instead of exerting pressure, gives electrical stimuli) and a thermode operating on a Peltier principle. The last procedure is a heat-evoked potential given to the subjects [25]. Recovery after SWS interruption produced a significant increase in mechanical pain thresholds. Recovery after REM sleep on the other hand did not significantly increase mechanical pain thresholds. Thermal pain threshold did not show significant differences between and within periods of sleep deprivation.

To evaluate the effect of total sleep deprivation on thermal pain thresholds and pain complaints, ten healthy volunteers were sleep deprived for two nights. The control group, which includes ten other healthy volunteers, had two undisturbed nights of sleep. Sleep interruption was done by a staff member, who monitored the subjects and ensured that the subjects stayed awake from 8:00 PM to 7:00 AM. Subjects participated in activities such as conversations, watching television, going for a walk, etc. Sensitivity of all subjects for cold and warmth sensation and cold and heat pain were then determined using a computer-controlled device that documented the responses the subjects had after being in contact with cold and warmth [26]. Cold and warmth stimuli were given utilizing a thermode attached to the skin of the forearm. Pain complaints were assessed by a pain questionnaire. A significant interaction between sleep deprivation and a decreased heat pain threshold during each single night was found, with a slight increase after recovery of sleep deprivation. The cold pain thresholds also decreased in the sleep deprived subjects. Sleep deprivation did not alter the detection thresholds for warmth and cold. As suggested in above described human studies, SWS deprivation makes individuals more sensitive to noxious stimuli. Recovery from SWS has the opposite effect. A higher pain perception is mostly seen when tested by pressure pain stimulation. The investigators themselves explain this finding by the fact that pressure pain stimulation targets both superficial and deep tissue, and muscle and skin nociception, whereas heat pain stimulation (used in their own study) targets primarily superficial tissue, and skin nociception [3, 27].

## 4 Mechanism of action

As noted in Box 1, pain perception is affected by more than one pathway. This section describes the mechanism of action of the most important pathways of pain and its relation to sleep (deprivation).

The two main pathways that carry nociceptive signals to higher centers in the brain are the spinothalamic tract and the spinoreticular tract. The first pathway mentioned consists of fibers projecting up the spinal cord and synapse when reaching the thalamus. From there, neurons ascend to terminate in the somatosensory cortex. This tract transmits signals that are important for pain localization. The second pathway mentioned is involved in the emotional aspects of pain. Neurons first synapse in the brain stem, before projecting to the thalamus, hypothalamus, and further to the cortex.

Pain perception is complex and subjective. It is affected by factors such as cognition, mood, beliefs, and genetics. Although the somatosensory cortex is important for the localization of pain, functional magnetic resonance imaging (fMRI) showed an activity of a large brain network during the experience of pain.

Inhibition of pain transmission is affected by two mechanisms. The first mechanism that acts to inhibit pain transmission is called the gate control theory of pain (ascending pathway). It describes a process of inhibitory pain modulation at the spinal cord level. By activating  $A\beta$  fibers with non-noxious stimuli, inhibitory interneurons in the dorsal horn are activated, what leads to inhibition of pain signals transmitted via C fibers. The second mechanism acts via descending inhibition from higher centers in the brain. The periaqueductal grey (PAG) in the midbrain and the rostral ventromedial medulla (RVM) contain high concentrations of opioid receptors and endogenous opioids, which is why opioids are analgesic. This pathway utilizes noradrenaline and serotonin as neurotransmitters [2, 28]. Both noted pathways are visualized in figure 2.

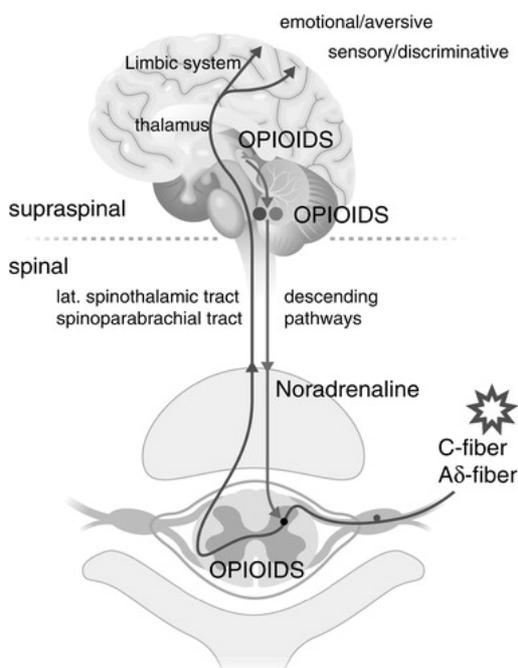


Figure 2. Ascending and descending pathways. Noradrenaline is in this review called norepinephrine, but are the same neurotransmitters. Serotonin is not mentioned in this figure, but its production in the locus raphe is located underneath the thalamus [29].

The remaining of this section will be about the opioidergic, serotonergic, norepinephrine and GABAergic pathways to identify the effect of sleep deprivation on the pain perception. A detailed explanation of these mechanisms is too profound for this review, but it is simply explained in order to answer the main question in this review.

#### 4.1 Opioidergic pathway

Opioids act by binding tightly and specifically to several types of opioid receptors in the brain. The brain produces endogenous morphine-like substances, called endorphins. Endorphins are particularly concentrated in areas that process or modulate nociceptive information and may produce analgesia (insensitivity for pain). Endorphin-containing neurons in the spinal cord and brain stem prevent the passage of nociceptive signals through the dorsal horn and into higher

levels of the brain where the perception of pain is generated [2]. Thus, opioids inhibit pain and are therefore analgesic.

According to an animal study performed in 1983, sleep deprivation may cause an inhibition of opioid protein synthesis and a reduced affinity of particular opioid receptors [30]. This study also used the 'flower pot technique' to carry out REM sleep deprivation in rats. After sleep depriving the rats, they had to undergo the cold-water-swim analgesia. During this technique, the rats were forced to swim five minutes in a bath filled with water with a temperature of 5°C. Next, pain threshold was measured by a pain sensitivity test according to the analgesiometric method (comparable with the paw pressure test). Responses to the pressure were determined by observing paw withdrawal or squeaking. Animals were injected with morphine, an opioid used to decrease pain perception, and their nociception was measured two hours after injection. Rats who were injected with morphine and that were sleep deprived both showed a decrease in analgesiometric scores. These results show that REM sleep disruption leads to a change in the opioidergic pathway and thus to an increase in pain perception.

#### 4.2 Serotonergic pathway

Serotonin (5-hydroxytryptamine [5-HT]) is released from platelets and mast cells after tissue injury. 5-HT receptors are present on C fibers (a type of nociceptor) and, in combination with other inflammatory mediators, 5-HT excites and sensitizes afferent nerve fibers, contributing to peripheral sensitization and hyperalgesia (increased sensitivity) [31]. Data suggests that a higher concentration of 5-HT leads to a higher pain perception. Subsequently, 5-HT promotes wakefulness.

The effect of sleep deprivation on serotonin levels in the brain was examined in a study [32] in which rats were sleep deprived for 8 hours. Serotonin was measured in the hippocampus and frontal cortex (brain regions associated with depression) in rats. It seemed that sleep deprivation produced a decrease in extracellular serotonin levels in both selected regions. Sleep deprived animals showed a lower concentration of serotonin than the control group. A study [33] investigating the effects of sleep deprivation on serotonin function in depression found that sleep deprivation produced an increase in 5-HT function in female depressed patients. In another study [34], fibromyalgia patients showed a lower level of serotonin in their bloodserum with respect to healthy controls. Unclear is what exactly caused this finding. In other words, do the serotonin levels increase, or does the sensitivity of the serotonin receptors change as a consequence of sleep deprivation? The animal study differs in outcome from the human studies described here. It appears that sleep deprivation alters the serotonin levels and (in human studies) increases pain. Not much research is done about the relationship between sleep deprivation, serotonin, and the effect on pain perception, but is needed in order to be able to give answer to the main question in this review.

#### 4.3 Norepinephrine pathway

Neurons containing norepinephrine have widespread connections in the brain. Noradrenergic projections to the cortex are involved in wakefulness and arousal and are thought to function to increase the brain's responsiveness [35]. In general, norepinephrine is known to have antinociceptive effects [36]. In some locations in the brain, it enhances pain when associated with tissue injury. Norepinephrine's effects depend on the type of adrenoceptor it works on,

where in the brain, and the duration of the pain stimuli [37]. The major source of norepinephrine is the locus coeruleus in the brain. Norepinephrine is important for maintaining normal sleep states. Adrenergic neurons (secreting norepinephrine) are activated during waking, have a lower firing rate during SWS and are silent during REM sleep [38].

Interestingly for this review, is the effect of sleep deprivation on the levels or mechanism of action of norepinephrine. It is seen that sleep deprivation increases firing of locus coeruleus neurons and thus increases levels of extracellular norepinephrine. In summary, sleep deprivation leads to a higher level of norepinephrine in the brain, which in turn leads to a higher pain perception. As mentioned here, the effect of norepinephrine depends on the location in the brain and other factors. For this reason, it cannot clearly be concluded what effect sleep deprivation in this pathway does with the pain perception [39,40].

#### 4.4 GABAergic pathway

GABAergic transmission is thought to be involved in the perception of pain and quality of sleep. GABA is ubiquitous and exists in high concentrations in the brain and spinal cord. It plays a major role as inhibitory neurotransmitter in the CNS. GABA<sub>A</sub> and GABA<sub>B</sub> receptors have different effects on pain perception and transmission, depending on the neurons they are located on and the area they are positioned in. In general, activation of either of the GABA receptors leads to an antinociceptive response. The GABA receptors thus tend to inhibit the propagation of pain impulses [17]. Evidence for this hypothesis was conducted in a study [30] observing a direct acting GABA receptor agonist to have antinociceptive properties. This again suggests that activation of GABA receptors inhibits pain. Mice were injected with the GABA receptor agonist after which nociceptive tests were performed. Nociceptive tests included tail-immersion (explained later in this review) and hot-plate methods. To perform the warm water tail-immersion test, the tail of the rat was immersed in water at a noxious temperature of 46°C, until tail withdrawal was observed. For the last method, mice were placed on a copper plate with a temperature of 50°C. Mice were unable to escape, as the plate was surrounded by walls. Behavior of the mice, like shaking their hind paw, was observed to determine pain. GABA uptake inhibitors also show antinociceptive effects. By inhibiting the uptake of GABA, GABA keeps activating GABA receptors, inhibiting pain.

Several generations of hypnotics are based on the inhibitory effects of GABA receptors, they decrease waking and increase SWS. During sleep, GABAergic neurons inhibit the arousal system, leading to a less interrupted sleep. GABAergic interneurons of the thalamus inhibit afferent input to the cerebral cortex, which includes nociceptive input [41]. These facts imply that GABA decreases pain and increases sleep. Experiments concluding GABA supplements or hypnotics (based on GABA's effects) contribute to better or less interrupted sleep. It is difficult to research whether pain thresholds increase due to a better night rest, or due to a high concentration GABA resulting from the supplements patients took. Clear is that GABA has antinociceptive effects in the body. The question relevant in this review is if sleep deprivation leads to a change in the GABA concentration (and thus to pain).

An animal study [42] in which rats were REM sleep deprived for 96 hours by the 'flower pot technique' was used to answer the question if sleep disruption has an effect on GABA levels in the brain. GABA contents in three different brain regions (frontal cortex, hypothalamus and brain stem) of the rat were measured utilizing high-performance liquid chromatography. The

sleep deprived rats showed an increase in GABA content. Another study [43] agrees with these findings. They tested rats' GABA contents after total sleep deprivation and also found an increase in GABA levels in the brain.

Earlier mentioned, GABA decreases pain and the number of arousal episodes during sleep. Deprivation of sleep does change GABA concentrations in the brain, but it is seen to increase GABA levels in rats. Because GABA in general increases sleep, one might expect a decrease in GABA content after sleep disruption. Definitely, GABA is involved in pain perception and sleep separately, but the main question in this review cannot be answered by this mechanism, because of the contradictory of these findings. More experiments are needed to prove a clear relationship – if existing at all – between sleep disruption, leading to changes in levels of GABA in the brain, what eventually may lead to pain.

## 5 Discussion

The goal of this review was to find out what the effect of sleep deprivation on pain perception is. As dated articles showed that pain enhances sleep disruption, a bidirectional relationship between the two was suggested. More recent studies presented evidence for the opposite relation: sleep deprivation leads to a higher pain perception. These findings suggest the existence of an ongoing cycle, in which the starting point is unclear. Recovery of sleep and sleep modifiers (pregabalin and sodium oxybate) improved pain perception. On the other hand, patients with an increased pain threshold had better night rests and less disturbed sleep.

Not all studies in this review were blinded, controlled studies, which makes the strength of their finding and conclusions discussable. Sleep was measured by polysomnography recordings, and SWS and REM sleep was deprived using different methods. After each sleep deprived night, subjects' pain threshold was measured by dolorimetry and analog scales. All studies showed a decrease in pain threshold, thus a higher pain perception, after a night of interrupted sleep. Chronic sleep deprivation (insomnia patients for example) showed the same effects as acute sleep deprivation did on pain perception. These results suggest that sleep disruption does point to a higher pain perception. As will be mentioned next, nociceptive and pain measurements are challenging to interpret, which is why the different influences of acute versus chronic pain are hard to distinguish. By all means, sleep recovery in fibromyalgia (chronic pain) does not show positive results regarding to pain as fast as sleep recovery in healthy subjects exposed to acute sleep deprivation does. Chronic sleep restriction will have stronger effects concerning pain than acute sleep restriction, mostly because of its ongoing, multifactorial cause of a disease (like fibromyalgia), that affects more than one specific type of pain or place in the body [6].

Dolorimetry used in human studies is a nonconcrete instrument, where subjects indicate their own pain. This may affect the validity of the studies performed. More evidence is needed to conclude this hypothesis, as not all findings were significantly proved. Besides using dolorimetry, studies referred to in this review did not take individual factors, such as age, gender, sex, and others, into account. A collection of studies examined the effects of these individual factors on sleep and pain separately, but never together. More research is needed, as these factors may influence the outcome of the experiments.

Both SWS and REM sleep were disrupted in separate studies. SWS was detected using EEG by identifying the delta waves. When delta waves (property of SWS) were detected, the subject's sleep was interrupted by applying physical methods. These studies called this sleep disruption 'selected SWS disruption' but did not mention the consequences of this technique. In 1999, a study [44] was performed to investigate SWS interruption. In this study, the SWS interruption technique (described above) and its concerns were explained. Using this technique to interrupt the SWS, the subject was prevented to fully enter stage 3 of NREM sleep by lightening its sleep but avoiding awakening the subject. As a result, REM sleep decreased, and the number of arousal periods increased. A very important point of discussion following this fact is whether or not the side effects of depriving SWS (decrease of REM sleep and increase in number of arousal periods) disturbed the outcome of the experiments. Strictly speaking, did SWS disruption influenced the increased pain perception or did the decrease in REM sleep or total sleep affect this. Furthermore, SWS disruption was conducted by determining delta EEG waves. REM sleep was mostly observed visually by observing subjects that showed REM sleep properties. SWS disruption is thus more reliably, and REM sleep could not emphatically be detected.

Opioidergic, serotonergic, norepinephrine, and GABAergic pathways are shortly mentioned in this review. For decades, the analgesic function of morphine is known. Sleep deprivation is proved to decrease morphine's action, meaning it increases pain perception by decreasing the affinity of opioid receptors. Sleep deprivation increases levels of serotonin, also leading to a possible increase of pain perception. Subsequently, sleep deprivation (almost always) leads to an increase in norepinephrine concentrations in the brain, similarly causing pain perception to increase in some parts of the brain. Lastly, interruption of sleep did show a change in GABA levels in some experiments but did not show one clear change in pain perception, as GABA is ubiquitous.

Conclusively, sleep deprivation leads to a higher pain perception according to the examined literature used in this review.

It is undeniable that pain is a very complicated system with several pathways that can be explained and that need to be considered when studying the relationship between sleep and pain. Like wisely, sleep is a complex phenomenon that up until now is not fully investigated. It is hard to focus on one aspect of pain at the time, as there are so many pathways and substances involved in the regulation of pain and sleep independently, but especially together. It is crucial to get a better understanding of the relation between sleep and pain, so patients dealing with sleep disruption caused by chronic pain (or the other way around) might be able to manage their disease.

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