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THE ROLE OF PAIN MODULATION IN NON-SUICIDAL SELF-INJURY

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The Role of Pain Modulation in Non-Suicidal Self-Injury

THESIS FOR DOCTORAL DEGREE (Ph.D)

By

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Whatever happened?

At once whatever happened starts receding.
Panting, and back on board, we line the rail
With trousers ripped, light wallets, and lips bleeding.

Yes, gone, thank God! Remembering each detail
We toss for half the night, but find next day
All's kodak-distant. Easily, then (though pale),

'Perspective brings significance,' we say,
Unhooding our photometers, and, snap!
What can't be printed can be thrown away.

Later, it's just a latitude: the map
Points out how unavoidable it was:
'Such coastal bedding always means mishap.'

Curses? The dark? Struggling? Where's the source
Of these yarns now (except in nightmares, of course)?

Philip Larkin

Till Nasse

POPULAR SCIENCE SUMMARY OF THE THESIS

Some individuals hurt themselves to cope with strong and negative emotions, for example by cutting or burning their skin. Psychiatric researchers call this behavior non-suicidal self-injury (NSSI). Many individuals with NSSI report that they feel little or no pain while self-injuring. This is also found in laboratory studies, in which the NSSI population demonstrates lower pain thresholds and higher pain tolerance. Reduced sensitivity to pain could be a risk factor for developing NSSI behavior, but we do not know why individuals with NSSI tend to experience less pain.

It has been found that individuals who are more sensitive to pain, such as individuals diagnosed with the pain syndrome fibromyalgia, exhibit deviations in how they modulate pain. Pain signals travel from pain receptors, through the spinal cord and into the brain. On each level, pain signals can be upregulated or downregulated. The pain system of individuals diagnosed with fibromyalgia tend to upregulate pain signals to a greater extent and downregulate pain signals to a lesser extent, with the effect that painful stimulation is experienced as more painful and that the pain is alleviated slower.

We believe that the reduced pain sensitivity found in the NSSI population could partly be explained by hyper-effective pain modulation. This means that the pain modulation system of individuals with NSSI is on the opposite side of a pain modulation spectrum of individuals diagnosed with fibromyalgia. If this is correct, the pain system of individuals with NSSI tend to upregulate pain signals to a lesser extent and downregulate pain signals to a greater extent.

To test this hypothesis, we recruited women with ongoing NSSI and tested them with methods developed to study pain modulation in patients with long-term pain. We also recruited a control group, including women without NSSI of the same age, in order to make comparisons with the NSSI group. In Study III, we used a test called conditioned pain modulation, that measures how painful stimulation on one part of the body modulates pain on another part of the body. In the same study we also tested how repeated pinprick stimulation is experienced because we know that the perceived pain tends to be upregulated with repeated stimulation. This test is called temporal summation. In Study IV, we used a pain testing protocol that was tested out on a non-clinical population in Study I. The protocol included painful heat stimulation, which was applied to the participants' legs, to study pain modulation. We also registered activity in the brain, during testing, using functional magnetic resonance imaging (fMRI). In the test, the temperature shifted slightly to produce disproportionate increase in pain (offset analgesia) and decrease in pain (onset hyperalgesia). The responses were compared between the NSSI group and a control group. Study II examined if self-administered pressure pain thresholds were higher compared with pressure pain thresholds administered by the experimenter. In this study we recruited healthy participants without NSSI. The effect, that self-induced pain is downregulated compared with externally induced pain, is called sensory attenuation and could also be relevant to understanding why individuals with NSSI report little or no pain while self-injuring. In addition, we tested if participants would experience sensory attenuation if they imagined that they self-administered pressure, during experimenter-administered pressure.

Our hypothesis, that the NSSI population has a hyper-effective pain modulation system, was supported by the results of the conditioned pain modulation test, because the NSSI group inhibited pain to a greater extent when exposed to painful stimulation on another part of the body, compared to the control group. Women with NSSI also upregulate pain to a lesser extent (onset hyperalgesia) during small changes in heat stimulation, compared to the control

group. Some of the results did not support our hypothesis. There was no difference between the groups in how they upregulated pain in the temporal summation test. Neither was there any difference in the inclination to downregulate pain during small changes in heat stimulation (offset analgesia). We also found that self-administered and imagined self-administered pressure pain thresholds were higher compared with pressure pain thresholds administered by the experimenter.

These results suggest that reports of decreased sensitivity to pain in the NSSI population is partly explained by how individuals with NSSI modulate pain, at least when it comes to women with NSSI. The fact that we only saw differences in pain modulation, between the NSSI group and the control group, in some of the pain tests could provide us with information about which pain modulation mechanisms to investigate in further studies, because we know from earlier studies that different tests measure different aspects of the pain modulation system.

ABSTRACT

Individuals with non-suicidal self-injury (NSSI) behavior tend to report feeling little or no pain when they self-injure. Moreover, in laboratory studies the NSSI population tends to demonstrate reduced sensitivity to painful stimuli. There is reason to believe that hypoalgesia could be a risk factor for developing and maintaining NSSI. Many theories have been proposed to explain the reduced sensitivity to pain in the NSSI population; some examples are dissociation, self-critical cognitive style, and low levels of endogenous opioids. However, the evidence supporting these theories are sparse. To understand why the NSSI population experiences less pain, there is a need for a better understanding of how individuals with NSSI process pain. We wanted to use methods that have been developed to study pain modulation in individuals with long-term pain to characterize the pain modulation system of women with ongoing NSSI. Our general hypothesis was that women with NSSI have a hyper-effective pain modulation system that inhibits pain to a greater extent and facilitates pain to a lesser extent, compared to women without NSSI.

In Study I, a non-clinical population ($N = 62$) was recruited to test a pain testing protocol in order to produce offset analgesia (OA) and onset hyperalgesia (OH). Small deviations in a painful thermal stimulation have been found to produce disproportional hypoalgesic (OA) and hyperalgesic (OH) responses. Different stimulus ranges (±1°C and ±2°C) were included in the protocol to study the dynamic relation between heat and pain. The study was composed of two identical experiments. In experiment 1, we produced OA and OH responses, using ±2°C but not ±1°C. In experiment 2, we only produced OA responses, but no OH responses.

Study II investigated if it was possible to induce sensory attenuation of pain in a non-clinical population ($N = 40$) by comparing self-administered pressure pain threshold to experimenter-administrated pressure pain threshold, using an algometer. An experimental condition, where the participants imagined that they pressed the algometer, was also included in the study, to examine if sensory attenuation could be induced with the help of imagery. Self-administered pressure was found to be less painful, compared to experimenter-administered pressure. Moreover, imagined self-administered pressure was also experienced as less painful than experimenter-administered pressure. Self-induced sensory attenuation of pain could be a factor in explaining hypoalgesia during NSSI.

Study III consisted of an extensive battery of pain tests in order to study pain modulation in a sample of women with NSSI ($N = 41$) and an age-matched control group, consisting of healthy women ($N = 40$). The study also included a simple pain test combined with fMRI. We found that the NSSI group demonstrated higher pressure and heat pain thresholds, compared to the control group. The NSSI group also demonstrated a larger conditioned pain modulation (CPM) effect, compared to the control group. CPM is a test based on the principle pain inhibits pain, and is a measure of central down-regulation of pain. We found no difference between the groups regarding temporal summation of pain, a measure of pain facilitation, or in heat pain tolerance. Tonic painful heat stimulation produced a larger hemodynamic response in primary and secondary somatosensory cortex in the NSSI group, compared to the control group.

In Study IV, we used the combined OA/OH protocol that was evaluated in Study I to study pain modulation in women with NSSI ($N = 37$) and controls ($N = 39$). The OA/OH protocol was combined with fMRI. Across groups, both the OA and the OH responses were significant. We also found a difference between the groups regarding the OH response, as the NSSI group demonstrated a weaker OH response, compared to the control group. The OH response was associated with a hemodynamic response in the primary somatosensory

cortex, across groups, which suggests that the nociceptive signal was upregulated before reaching the brain.

In line with our main hypothesis, we found that the NSSI group inhibited pain to a greater extent (CPM in Study III) and facilitated pain to a lesser extent (OH in Study IV), compared to the control group. These results suggest that women with NSSI have a hyper-effective pain modulation system. There were also results that did not support our main hypothesis; the NSSI group did not demonstrate weaker pain facilitation when tested with the temporal summation protocol (Study III) or stronger inhibition associated with OA (Study IV). An explanation could be that different pain tests measure different aspects of pain modulation and only certain pain modulation mechanisms are affected in the NSSI population. The studies of this thesis provide evidence that the previous findings of hypoalgesia in the NSSI population does not reflect response bias but is rooted in how the nervous system modulates nociceptive signals.

LIST OF SCIENTIFIC PAPERS

I. **Fust, J.**, Lalouni, M., Vadenmark-Lundqvist, V., Wärnberg, E., & Jensen, K. B. (2021). Offset analgesia and onset hyperalgesia with different stimulus ranges. *Pain reports*, *6*(1).
II. Lalouni, M., **Fust, J.**, Vadenmark-Lundqvist, V., Ehrsson, H. H., Kilteni, K., & Jensen, K. B. (2021). Predicting pain: Differential pain thresholds during self-induced, externally induced, and imagined self-induced pressure pain. *Pain, 162*(5), 1539.
III. Lalouni, M., **Fust, J**., Bjureberg, J., Kastrati, G., Fondberg, R., Fransson, P., Jayaram-Lindström, N., Kosek, E., Hellner, C., & Jensen, K. B. (2022). Augmented pain inhibition and higher integration of pain modulatory brain networks in women with self-injury behavior [Unpublished manuscript].
IV. **Fust, J.**, Lalouni, M., Kastrati, G., Thompson, W. H., Bjureberg, J., Jayaram-Lindström, N., Kosek, E., Hellner, C., Fransson, P., & Jensen, K. B. Offset analgesia and onset hyperalgesia: A comparison between individuals with non-suicidal self-injury and a control group [Unpublished manuscript].

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Santoft, F., Axelsson, E., Öst, L. G., Hedman-Lagerlöf, M., **Fust, J.**, & Hedman-Lagerlöf, E. (2019). Cognitive behaviour therapy for depression in primary care: systematic review and meta-analysis. *Psychological medicine*, *49*(8), 1266-1274.
II. Pontén, M., **Fust, J**., D'Onofrio, P., Dorp, R. V., Sunnergård, L., Ingre, M., ... & Jensen, K. (2019). The pain alarm response-an example of how conscious awareness shapes pain perception. *Scientific reports*, *9*(1), 1-8.
III. Tacikowski, P., **Fust, J.**, & Ehrsson, H. H. (2020). Fluidity of gender identity induced by illusory body-sex change. *Scientific reports*, *10*(1), 1-14.
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V. Hedman-Lagerlöf, E., **Fust, J.**, Axelsson, E., Bonnert, M., Lalouni, M., Molander, O., ... & Bradley, M. (2021). Internet-Delivered Cognitive Behavior Therapy for Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology*, *157*(7), 796-804.

CONTENTS

LIST OF ABBREVIATIONS

BPD	Borderline personality disorder
CPM	Conditioned pain modulation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
fMRI	Functional magnetic resonance imaging
Hz	Hertz
kPa	Kilopascal
NRS	Numeric rating scale
NSSI	Non-suicidal self-injury
OA	Offset analgesia
OH	Onset hyperalgesia
QST	Quantitative sensory testing

1 INTRODUCTION

Self-harm is a puzzling behavior. Why would someone willingly tear up their skin with a razorblade or put a cigarette lighter under their arm? Just the thought of these acts makes most people experience discomfort. In common with all other organisms on earth, we are designed by evolution to avoid tissue damage. Bodily harm will reduce our chances of survival and could in some cases lead to our imminent death. That is why pain is such a strong internal signal—a signal that usually overrides all other motivations.

From a learning perspective, the benefits of self-harm behavior must somehow exceed the high cost of pain, otherwise the behavior would not persist. For most people there is no direct benefit of self-harm, but for a person in severe distress and with a limited number of other options, self-harm behavior, such as self-cutting, can function as both a means to regulate negative emotions and to signal distress to other people. There is clear evidence that individuals with self-harm behavior both suffer from strong negative emotions and tend to lack effective coping strategies (McKenzie & Gross, 2014). But there are also many people with these traits that do not develop self-harm behavior. So, what sets individuals with self-harm behavior apart from individuals without self-harm behavior in the psychiatric population?

There is reason to believe that the development and maintenance of self-harm behavior is explained, not only by the benefits of self-harm, but also by the reduced cost of the self-harm. According to *the benefits and barriers model* of non-suicidal self-injury by Jill Hooley and Joseph Franklin (2018), it is primarily the reduced barriers to hurting oneself that explain the maintenance of self-harm behavior. Physical pain is one of these barriers. We know from large-scale studies that individuals with self-injurious behavior often report feeling little or no pain while they are self-harming (Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007). If self-harm is less painful then it is also less costly for the individual, with the effect that the benefits of self-harm are more likely to tip the scale.

Even though pain could be an important factor explaining self-harm behavior we still know little about the relationship between self-harm and pain. We do know that hypoalgesia (reduced pain-sensitivity) is not specific to the act of self-harm, but rather a stable trait in the self-harm population. Individuals with self-injurious behavior are not only insensitive to pain when they hurt themselves but experience in general less pain than the general population. This has been demonstrated in experimental studies with several pain modalities and pain testing methods (Kirtley, O'Carroll, & O'Connor, 2016; Koenig, Thayer, & Kaess, 2016). However, it is not clear if this trait precedes self-harm behavior or rather is developed by repeated exposure to pain.

It is also not known how the pain system of individuals with self-injurious behavior differs from the general population. People in general vary in their capacity to up- and downregulate pain, which means that the response to incoming nociceptive signals differs greatly between individuals. Pain modulation is dysfunctional among patients with long-term pain, for example patients diagnosed with fibromyalgia and osteoarthritis (Yarnitsky, Granot, & Granovsky, 2014). There is preliminary evidence that individuals with self-injurious behavior I are located at the opposite side of the pain modulation spectrum compared to those who suffer from long-term pain (Defrin et al., 2020). That is, the prevalence of hypoalgesia in the self-harm population could partly be explained by hyper-effective pain modulation: a propensity to downregulate nociceptive signals.

2 LITERATURE REVIEW

2.1 NON-SUICIDAL SELF-INJURY

Before we dwell deeper into the relationship between self-harm and pain, I would like to give a short introduction to self-harm behavior. There are many behaviors that could be categorized as self-harm. I will focus on a subset of self-harm behaviors that is called *non-suicidal self-injury* (NSSI). As the term suggest, NSSI is distinct from self-harming behavior with suicidal intent. Moreover, NSSI must result in some type of tissue damage, which differentiates NSSI from self-destructive behavior, which is harmful for the person, but does not, at least not directly, cause bodily harm (Klonsky & Muehlenkamp, 2007).

Studies on NSSI-type behavior have historically been conducted on individuals with borderline personality disorder which is a patient group with high prevalence of NSSI behavior. However, during the last ten years more and more research has studied NSSI as a transdiagnostic construct. It has even been proposed that NSSI should be a new diagnostic entity in its own right. Suggested criteria for a future NSSI disorder include engagement in NSSI on five or more days within the past year, and the expectation that NSSI will provide emotional or cognitive relief, resolve an interpersonal difficulty, and/or create a positive feeling state (American Psychiatric Association, 2013).

There are multiple methods and functions of NSSI. Common NSSI methods are cutting, scratching, and burning the skin, and hitting oneself (Anestis, Khazem, & Law, 2015; Zetterqvist, Lundh, Dahlström, & Svedin, 2013). The severity of the tissue damage ranges from superficial wounds to severe damage that will require hospital care and even plastic surgery (Larkin, Corcoran, Perry, & Arensman, 2013). Usually, individuals with NSSI give multiple reasons why they hurt themselves. Nock & Prinstein (2004) have argued that the functions of NSSI could be divided into two broad categories depending on how the behavior is reinforced: intrapersonal, if the function of the behavior is to change current thoughts and feelings (e.g., distracting from negative thoughts); and interpersonal, if the behavior is directed towards the social environment (e.g., signaling distress). Usually, individuals with NSSI give multiple reasons why they hurt themselves, but intrapersonal functions tend to be more frequently reported (Nock, 2010).

NSSI is especially prevalent among young women. In a Swedish study (N = 3,060), 56.2% of the women aged 15-17 reported NSSI behavior, and 11.1% were deemed to fulfill the proposed DSM-5 criteria for NSSI disorder (Zetterqvist, Lundh, Dahlström, & Svedin, 2013). NSSI is also prevalent in the psychiatric population, especially in groups with negative emotionality and difficulties regulating emotions such as borderline personality disorder (Klonsky, Victor, & Saffer, 2014).

2.2 REPORTS OF REDUCED PAIN SENSITIVITY

The majority of individuals with NSSI report that they feel little or no pain during NSSI. This has been consistently found in different populations, for example in community samples including adolescents in United States (Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007), Sweden (Zetterqvist, Lundh, Dahlström, & Svedin, 2013), and Iran (Izadi-Mazidi, Yaghubi, Mohammadkhani, & Hassanabadi. 2019).

Individuals with more frequent NSSI behavior tend to report more pain while they self-injure compared to those who only report few incidents of NSSI (Loyd-Richardson et al., 2007; Zetterqvist, Lundh, Dahlström, & Svedin, 2013). This finding seems to be in conflict with the association between hypoalgesia and NSSI, but is probably explained by the severity of the tissue damage, where more severe wounds would trigger more pain. For example, persons with frequent NSSI report to a greater extent being given medical treatment for the injuries than persons with less frequent NSSI (Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007).

2.3 STATE-DEPENDENT HYPOALGESIA

One possible explanation of the reports of lack of pain during NSSI is that the emotional state during the act of self-harm is affecting the ability to experience pain, suggesting a state-dependent mechanism of hypoalgesia in NSSI. As already mentioned, individuals with NSSI exhibit both negative emotionality and emotional dysregulation. We also know that high physiological arousal can reduce pain intensity. This is demonstrated in the research of stress-induced analgesia (Butler & Finn, 2009) and exercise-induced analgesia (Koltyn, 2000).

There are some studies suggesting that emotional arousal could explain the attenuated pain response during NSSI. In a laboratory study by Bohus et al (2000) female BPD patients with NSSI experienced slightly less pain during pain testing when they were under distress than when they reported feeling calm. In another laboratory study, high pain thresholds were positively correlated with self-reported aversive arousal (Ludäscher et al., 2007).

2.4 TRAIT-DEPENDENT HYPOALGESIA

There is strong evidence that the reports of hypoalgesia reflect a stable hypoalgesic trait in the NSSI population. It is important to note that trait-dependent hypoalgesia is not in conflict with state-dependent hypoalgesia. Even if individuals with NSSI feel less pain in general this trait can be enhanced by state-dependent factors, such as emotional arousal.

Koenig, Thayer, and Kaess published a meta-analysis 2016 that compiled studies of pain sensitivity of individuals with self-injurious behavior. The meta-analysis included a total of 67 comparisons between individuals with NSSI and healthy controls from 32 studies. These comparisons were divided into three different types of measurements of pain sensitivity: pain threshold (the onset of pain), pain tolerance (the maximum endurance of pain), and pain intensity (the rating of a painful stimulus). The majority of the studies used some kind of hot or cold thermal stimulation to induce pain, but there were also comparisons based on other stimulus modalities, such as pressure and electric stimulation. Koenig, Thayer and Kaess found that individuals with NSSI deviated from healthy controls on all three measurements. The pain threshold of individuals with NSSI was higher (0.76), they tolerated more pain (0.47), and rated painful stimuli as less painful (-0.68), compared to healthy controls (effect sizes were calculated as Hedges' *g*).

Studies that have been conducted after the meta-analysis have found significant difference between individuals with NSSI and healthy controls regarding pain thresholds and pain tolerance (Funkhouser et al., 2019; Koenig et al., 2017A; Koenig et al., 2017B; Miglani, Chavan, & Gupta, 2021), except in a recent study where they found a significant difference in pain tolerance, but not in pain threshold (Tuna & Gençöz, 2020), and a study by van der Venne (2020), in which they found significant differences in pain threshold, but not in pain

tolerance. Interestingly, several recent comparisons using pain intensity (ratings of painful stimuli) have not detected a significant difference between individuals with NSSI and healthy controls (Naoum et al., 2019; Koenig et al., 2017A; Koenig et al., 2017B; Willis et al., 2017).

A lot of effort has been put into isolating variables that can explain the hypoalgesic trait in the NSSI population. In the meta-regression that is included in the meta-analysis by Koenig, Thayer and Kaess (2016) they found that age and sex explain some of the variance in the dataset. This is not surprising given that this pattern is also found in the general population (i.e., men and older people tend to be less sensitive to pain). They also found that individuals with NSSI and BPD display higher pain thresholds and pain tolerance compared to individuals with NSSI, without BPD diagnosis (Koenig, Thayer, & Kaess, 2016).

It is not clear if the difference in pain sensitivity between the BPD and non-BPD group is explained by higher frequency of NSSI in the BPD group, or if individuals with BPD differ from individuals without BPD in some other way. It has been hypothesized that reduced pain sensitivity could be the effect of general perceptual deviations in the BPD population, but researchers have not been able to find any other interoceptive or exteroceptive differences between individuals with BPD and healthy controls (Hart, McGowan, Minati, Critchley, 2013; Malejko et al., 2018). Dissociation has also been proposed as a mediating link between BPD and hypoalgesia. Dissociation is a complex (and maybe not very well-defined) construct that includes symptoms such as depersonalization, derealization, emotional numbing, memory fragmentation, and somatoform symptoms (Krause-Utz, Frost, Winter, & Elzinga, 2017). Dissociative symptoms are often reported by BPD patients and are one of the diagnostic criteria for BPD in DSM-5. There are even researchers suggesting that hypoalgesia could be defined as a dissociative trait per se (Defrin et al., 2020), but the evidence for an association between dissociation and hypoalgesia/analgesia is sparse (Kirtley, O'Carroll, & O'Connor, 2016).

Self-criticism is another psychological trait that has been proposed to link NSSI and hypoalgesia together. Hooley et al (2010) found that negative beliefs about one's self-worth predicted pain tolerance in participants with NSSI behavior. This finding has later been replicated by the same research group (Fox, Toole, Franklin, & Hooley, 2017; Hooley & Germain, 2014). However, one study did not find a significant link between self-criticism and pain sensitivity (Fox, Sullivan, Wang, & Hooley, 2019). It is not clear why self-critical beliefs would decrease pain sensitivity. One explanation that has been put forward is that self-criticism alters the affective component of pain (Fox, Sullivan, Wang, & Hooley, 2019).

2.5 THE ROLE OF ENDOGENOUS OPIOIDS

The role of endogenous opioids in self-harm behavior has been discussed for decades (Coid, Allolio, & Ress, 1983; Russ et al., 1994; Bresin, & Gordon, 2013). Endogenous opioids have a central role in pain modulation (Dickenson, 1991; Fields, 2004). In addition, endogenous opioids are thought to be involved in regulating emotional "pain" (Zubieta et al., 2001). According to the homeostasis model of NSSI proposed by Stanley et al. (2010), individuals with NSSI suffer from chronically low levels of endogenous opioids which results in maladaptive response to stress. The function of self-harm is to raise the levels of endogenous opioids to downregulate stress.

Currently, the empirical support for this model is not very strong. While there are studies that have found lower levels of endogenous opioids in individuals with NSSI and BPD patients, compared to healthy controls, there are also studies that found elevated levels of endogenous

opioids in the self-harm population (Bresin, & Gordon, 2013). In a recent study, including 94 adolescents with NSSI, no significant correlations between plasma beta-endorphins (a marker of endogenous opioid release) and pain threshold, pain intensity, and pain tolerance were found (van der Venne et al, 2020).

Moreover, the association between endogenous opioids and hypoalgesia is not clear. If it is true that individuals with NSSI have lower levels of endogenous opioids, would they not rather experience unusually high levels of pain? One explanation that has been put forward is that lower levels of endogenous opioids lead to sensitization of opioid receptors, which increase the analgesic response to endogenous opioids released during nociceptive stimulation (Bresin & Gordon, 2013). There is a lack of studies using experimental manipulation to test the association between endogenous opioids and hypoalgesia in the NSSI population. In one study, BPD patients with a history of self-harm behavior were given either naloxone, an opioid antagonist, or saline injection as placebo, before pain testing, but there were no significant differences in the pain responses between the groups (Russ et al., 1994).

2.6 DO INDIVIDUALS WITH NSSI HAVE AN ANTINOCICEPTIVE PAIN MODULATION PROFILE?

The experience of pain often includes activation of the peripheral pain receptors, but also includes processing further up the neural axis in the brain and the spinal cord. These mechanisms can modulate the pain experience, by facilitating and inhibiting the signals from pain receptors. Long-term pain is often associated with changes in the central nervous system, which can lead to attenuated inhibition and/or enhanced facilitation of pain signals. By using psychophysical pain testing protocols—so called *quantitative sensory testing* (QST)—pain researchers have been able to isolate pain modulatory subsystems. For example, it has been suggested that manipulations of endogenous opioids have a large influence on the wind-up phenomenon related to the QST protocol temporal summation: a pain test where repeated stimulations lead to increased pain intensities. However, opioid antagonists have no effect on the hypoalgesic response elicited by the offset analgesia protocol (Hermans, Calders, Van Oosterwijck, Verschelde, Bertel, Meeus, 2016): a pain test where the brief increase of an ongoing painful stimulation leads to decreased pain when stimulation return to baseline level.

According to Yarnitsky, Granot, and Granovsky (2014), multiple pain testing protocols can be used to characterize individuals' pain modulation profiles on a spectrum between pronociception (i.e., high pain facilitation and low pain inhibition) and antinociception (i.e., low pain facilitation and high pain inhibition). For example, an individual with a pronociceptive phenotype is likely to facilitate pain when tested with the temporal summation protocol (increased pain) and fail to inhibit pain when tested with conditioned pain modulation (CPM) protocol (decreased pain). A pronociceptive pain profile can be seen as a sign of ongoing long-term pain but also as a risk factor for developing long-term pain in the future. Conversely, Yarnitsky, Granot, and Granovsky (2014) suggest that an antinociceptive pain modulation profile is a protective factor for developing long-term pain. But there is reason to believe that an antinociceptive pain modulation profile could instead be a risk factor for developing NSSI behavior in patients with negative emotionality.

In a study by Defrin et al. (2020), female BPD patients were tested with psychophysical pain testing protocols used to study pain modulation in long-term pain patients. While they did not find any differences between the BPD group and healthy controls' responses to the temporal summation protocol (increased pain), they did find evidence of increased pain inhibition in the conditioned pain modulation protocol (decreased pain). Furthermore, the

BPD group also habituated faster to tonic heat stimulation compared to the control group. It is important to note that only about half of the BPD group reported NSSI. Also, the study had low statistical power, including only 22 participants in the BPD group in an experimental setting where the effect sizes are generally moderate.

In a recent study by Leone et al. (2021), 30 adolescents (age 11-18 years) with NSSI and age-matched control group including 20 participants underwent a series of pain tests, including a version of the conditioned pain modulation protocol. In contrast to Defrin et al. (2020), they found that the NSSI group demonstrated reduced conditioned pain modulation response, compared to the control group. It is not clear why Leone et al. (2021) found the opposite results, compared to Defrin et al. (2020). It could be explained by the clinical samples included in the studies. While Defrin et al., (2020) recruited adult BPD patients, Leone et al., (2021) included adolescents with NSSI behavior. It could also be explained by the differences in the CPM protocols used by the two studies.

In sum, there are few attempts to characterize the pain regulatory system in individuals with NSSI and the results have so far been conclusive, mainly due to heterogeneous participants and low statistical power.

3 RESEARCH AIMS

The general aim of this thesis was to study the contribution of endogenous pain modulation to hypoalgesia in the NSSI population. Study I and II included a non-clinical sample in order to investigate pain modulatory processes relevant to the NSSI population and to make preparations for pain testing on a NSSI population. Study III and IV included female participants with ongoing NSSI and a control group, consisting of healthy age-matched women.

Study I
The aim of Study I was to replicate a finding of Alter et al., (2020) that an inverted *offset analgesia* (OA) protocol will produce a hyperalgesic response, called *onset hyperalgesia* (OH), and also investigate the effect of different stimulus ranges (±1-2°C) on the OA and OH responses. This study was a pilot study in preparation for Study IV. In the study we tested different versions of the OA and OH protocol on a non-clinical population.

Study II
In Study II we compared the pain thresholds of a non-clinical population in relation to experimenter-administered, self-administered, and imagined self-administered pressure pain. The aim of the study was to study self-attenuation of pain (inhibition by self-administration), which could be a relevant mechanism for the understanding of hypoalgesia in the NSSI population.

Study III
In Study III we used a standard QST protocol, including pain thresholds, temporal summation, and conditioned pain modulation to characterize the pain modulatory system of women with NSSI, compared to a non-clinical sample. The study also included a pain test combined with fMRI in order to explore the neural correlates of heat pain in the two groups.

Study IV
In Study IV, we developed a new version of the OA/OH protocol, based on the results of Study I, that was used to study downregulation and upregulation of heat pain in a NSSI sample and a control group in Study IV. In this study, the pain testing was conducted inside a MR camera to collect functional brain data.

4 MATERIALS AND METHODS

4.1 OPEN SCIENCE PRACTICES

Study I was not pre-registered since it was unclear how to analyze the data. Primarily, because we did not know during which time interval we were able to detect a potential OH effect. Therefore, experiment 1 of Study I was defined as exploratory. To confirm the results of experiment 1 we decided to run another experiment. Based on the distinction between exploratory and confirmatory experiments proposed by Wagenmakers et al., (2012), it could be argued that experiment 2 should not be defined as confirmatory, because we did not pre-register the hypothesis or analysis plan. This was a mistake from our side. Study I was first published as a preprint on medRxiv:
https://www.medrxiv.org/content/10.1101/2020.06.01.20113613v1.article-metrics. All code that was used in Study I was shared on open science framework: https://osf.io/uh678/.

Study II was not pre-registered, but the analysis plan was registered on open science framework before we analyzed the data: https://osf.io/ra9ug. None of the code that was used in the study was shared publicly.

In Study III, we pre-registered the hypotheses and analysis plan for the QST protocol, but the fMRI part of the study was not pre-registered and defined as exploratory. The study was published as a preprint on medRxiv:
https://osf.io/sbz4m. The code that was used to analyze the QST data was shared on open science framework: https://osf.io/gujwt/.

No data was shared publicly from any of the studies included in this thesis.

4.2 ETHICAL CONSIDERATIONS

There are two important major ethical considerations that we had to take into account when working with studies of this thesis. First, we studied a sensitive psychiatric population. Second, we used experimental pain stimulation.

Because the NSSI population have an increased risk of suicide we have been very careful not to include participants that exhibits what we call active suicidality. Our exclusion criteria stated that NSSI participants may not have a history of suicide attempts or suicide plans during the last year. This was checked with a questionnaire during the initial screening process, and later, followed-up by a face-to-face suicide screening during the first visit, conducted by clinical psychologist and NSSI researcher Johan Bjureberg. During this visit, Johan also explained the study procedure and made sure that the participant had a safety plan if they experienced adverse effects of the study.

Experimental pain research needs special ethical considerations. According to *International Association of the Study of Pain's* ethical guidelines for pain research in humans, it is important that stimuli do not exceed what the participants can tolerate and that the participants can terminate the painful stimuli any time they want. We made an effort to follow these guidelines carefully. We used perception-guided pain calibration to measure the pain sensitivity of each participant. This let us use that absolute minimum of stimulation that we needed to get the levels of pain needed for the study. We gave both written and verbal instructions to all participants that they could cancel their participation at all times, without

providing any particular reason. Before every test, we explained to the participant that we would terminate the stimulation if they gave us a verbal signal. We also checked with the participants continuously during testing. After the testing, Maria Lalouni, who is also a clinical psychologist, talked with the participants about their experiences during the testing and made sure the participants were not experiencing any adverse effects. If necessary, the safety plan from the initial assessment could be recalled. However, this was never needed during the study.

The regional Ethics Review Board in Stockholm approved the study (Dnr: 2018/1367-31/1). Supplements to the ethical permission were later approved by the board (Dnr: 201812115-32, 2019-03076, and 2019-03318).

4.3 PARTICIPANTS

In experiment 1 of Study I, we decided to only recruit women between the age 18-35 years. The reason was that we planned to recruit participants of the same age in Study III and IV. We also specified in the advertisement for the study that the participants were supposed to be in good health. In experiment 2 of Study II, we widened the inclusion criteria to also include men to be able to generalize the results to a broader population. The participants of experiment 2, in Study I, also took part in Study II.

In study III and IV, we recruited a group of individuals with ongoing NSSI and an age-matched control group. The general inclusion criteria were: (a) woman, (b) age 18-35 years, and (c) right-handed. The general exclusion criteria were: (d) chronic inflammatory, autoimmune, or other somatic disorder requiring treatment, (e) pain condition, (f) contraindication for fMRI (e.g., metal implant, pregnancy, claustrophobia), (g) suicide attempts during the last year, (h) suicidal plans or acute risk for suicide. Specific inclusion criteria for participants with NSSI: (i) self-injury $\geq$ 5 days during the last year. Specific exclusion criteria for controls: (j) treatment for depression or anxiety.

4.4 OFFSET ANALGESIA

Offset analgesia (OA) is a disproportional reduction of pain following a short increase and a subsequent decrease of an already painful thermal stimulation. This effect was first demonstrated by Grill & Coghill (2002), who compared the OA effect to contrast enhancement of the visual system. Studies on OA tend to stay close to the protocol set by Grill & Coghill, using thermal stimulation and comparing an OA condition—with a ±1°C shift from baseline midway through the stimulation—to a constant painful stimulation (Szikszay et al., 2019). Pain intensity is usually rated continuously during the thermal stimulation. The OA effect is believed to be related to both peripheral and central mechanisms in the pain system (Ligato et al., 2018), although the OA effect has not been successfully manipulated by pharmacological interventions (Larsen, Uth, Arendt-Nielsen, & Petersen, 2021). The OA effect is often reduced in populations with long-term pain. In Study I, we compared the original ±1°C OA to a ±2°C OA and found that a ±2°C shift in temperature produced larger OA effects. In order to increase statistical power we decided to use ±2°C OA in Study IV.

4.5 ONSET HYPERALGESIA

Onset hyperalgesia (OH) could be viewed as the opposite effect of OA. Instead of an upward shift in temperature, OH is produced by a short decrease in temperature, which leads to a disproportionate increase in pain intensity, when the temperature returns to baseline. This OH effect was first presented in a paper by Alter et al. (2020). Based on the results of Study I, we decided to use a OH protocol with a ±2°C shift in temperature in Study IV (Alter et al., 2020 used a ±1°C shift).

4.6 CONDITIONED PAIN MODULATION

Conditioned pain modulation (CPM) is a pain testing protocol based on the principle "pain inhibits pain". The test is associated with a pain modulatory pathway discovered in rodents called diffuse noxious inhibitory control (Le Bars, Dickenson, & Besson, 1979). During the test, participants are exposed to two painful stimuli on different parts of the body. The stimuli is either given at the same time or in a sequence. The participants are only rating one of the stimuli, called the test stimulus. The other stimulus, called the conditioning stimulus, is modulating the test stimulus. The average response, in healthy populations, is to experience the test stimulus as less painful in combination with the conditioning stimulus than without the conditioning stimulus. Similar to offset analgesia, the CPM effect has been found to be reduced in populations with long-term pain (Yarnitsky, Granot, & Granovsky, 2014). In Study III we used a version of the CPM protocol where ischemic inducing pressure on the right arm was the conditioning stimulus and pressure pain threshold on the left calf was the test test stimulus.

4.7 TEMPORAL SUMMATION

The temporal summation protocol measures central aspects of pain facilitation. During the test, repeated stimulation with a noxious stimulus is given in one location of the body, usually at the speed of 1 Hz. Even though the stimulus intensity is kept constant, participants tend to experience a "wind-up" in pain intensity over time. This wind-up effect tends to be more pronounced in patients with long-term pain, such as fibromyalgia (Yarnitsky, Granot, & Granovsky, 2014). Temporal summation can be produced with different stimulus modalities, the most common are heat and pinprick stimulation, which creates a sensation of being pricked with a needle without piercing the skin. In Study III we used a temporal summation protocol with pinprick stimulation.

4.8 PAIN INTENSITY

Pain intensity is the self-reported intensity of pain. It is usually measured with a numerical rating scale or with a visual analogue scale. Pain intensity scales tend to have at least two endpoints, which are presented to the participants in writing or verbally. In all the studies of the thesis we have used a *numeric rating scale* (NRS) ranging from 0 to 10 (see figure 1). Participants have been instructed that 0 means "no pain" and 10 means "worst imaginable pain". Often the ratings have been given on a computer screen using a trackball, and sometimes the ratings have been given by the participants verbally to the experimenter.

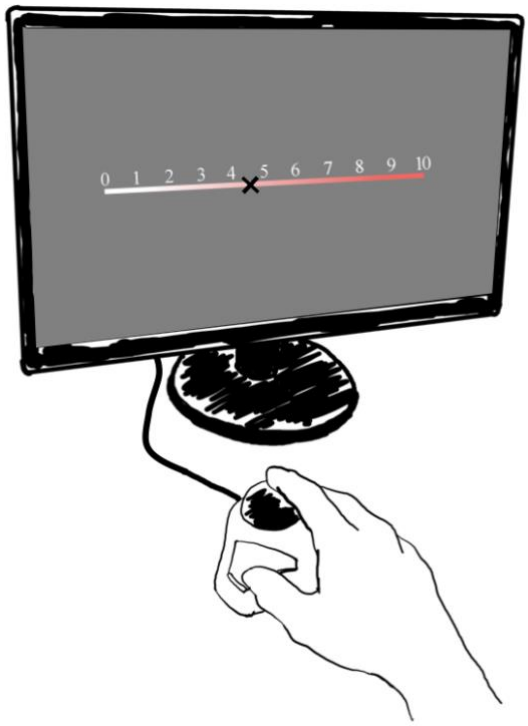

Figure 1. The numeric rating scale used to rate pain intensity in the studies.

4.9 PAIN THRESHOLD

Pain threshold is defined as "the first barely perceptible pain to appear in an instructed subject under given conditions of noxious stimulation" (Beecher, 1957). This means that the scale of pain thresholds is the intensity of the noxious stimulation, not the pain intensity. In Study III we used both pressure and heat to estimate pain thresholds. In Study II only pressure pain thresholds were assessed. Pressure pain threshold was estimated by gradually increasing pressure with algometer, i.e., the method of limits. Heat pain threshold was measured with a more complex procedure in which stimulus intensity was randomized, to avoid response biases.

4.10 PAIN TOLERANCE

Pain tolerance is usually defined as the maximum stimulus intensity a person can tolerate. A common method to measure pain tolerance is the cold pressor task, in which a person is instructed to keep the hand in cold water as long time as possible. Due to ethical concerns, we do not want to reach the participants' pain tolerance during pain testing, instead we define pain tolerance as NRS 6/10 in Study III.

4.11 FUNCTIONAL MAGNETIC RESONANCE IMAGING

fMRI is an imaging technique to measure changes in the hemodynamic response (i.e., the blood oxygenation, in the brain). The technique is common in cognitive neuroscience because the hemodynamic response is an indirect measure of neuronal activity. Compared to electroencephalography, the other of the two most popular imaging techniques, fMRI has

poor temporal resolution (in our studies the sampling time was over 2 seconds), and relatively good spatial resolution. The raw data needs to be preprocessed before it can be analyzed. After this step, the hemodynamic response is combined with a structural image of the participants' brains and a standard brain, resulting in an image that consists of multiple 3D pixels or *voxels*, often in the size of 3 mm^3. Importantly, we used task-based fMRI, which means that we looked at the hemodynamic response in the brain during tasks. The tasks in our studies included pain stimulation. We then contrasted the hemodynamic response to the hemodynamic response during control conditions, to subtract the hemodynamic response unrelated to the task.

5 SUMMARY OF STUDIES

5.1 STUDY I

5.1.1 Methods

In Study I, we evaluated a combined OA and OH protocol on a non-clinical population in two identical experiments. The first experiment was exploratory, the second was confirmatory regarding the results in the first experiment. The first experiment included only female participants ($N = 21$). In the second experiment we recruited participants of both sexes ($N = 41$, 22 women). We used a slightly modified version of the OH protocol, used by Alter et al., (2020). We also added two extra OA and OH conditions with ±2°C stimulus range during T2 (see figure 2), in addition to the traditional ±1°C stimulus range. The OA and OH conditions were compared to constant painful stimulation. This means the experiment included 5 conditions ($OA_{1℃}$, $OA_{2℃}$, $OH_{1℃}$, and $OH_{2℃}$, and control). We used a thermal stimulator to produce heat pain on the participants' left calf. The baseline temperature during time intervals T1 and T2 were individually calibrated before the experiments. During testing, participants rated their pain intensity continuously with a NRS scale (0-10) on a screen, using a trackball. OA and OH responses were calculated by comparing experimental conditions to the control condition during a 13 second time interval at the end of T3. Statistical tests were made using repeated measures ANOVA and post-hoc paired t-test, corrected with the Benjamini-Hochberg method.

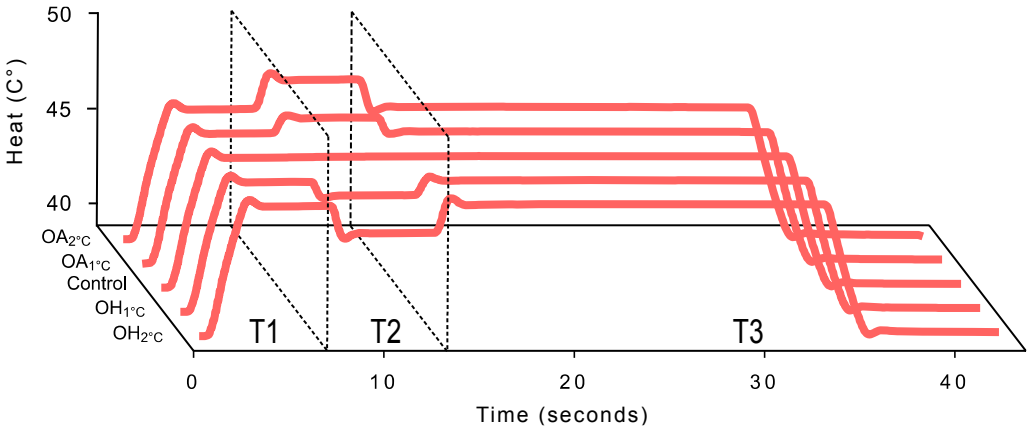

Figure 2. Mean heat stimulation (℃) during the different conditions of the OA/OH protocol in Study I.

5.1.2 Results

In experiment 1, we found a significant OA effect and OH effect in the ±2°C conditions ($OA_{2℃}$ and $OH_{2℃}$), but not during the ±1°C conditions ($OA_{1℃}$ and $OH_{1℃}$). In experiment 2, we found significant effects during the OA conditions ($OA_{1℃}$ and $OA_{2℃}$), but not during any of the OH conditions ($OH_{1℃}$ and $OH_{2℃}$). Exploratory analysis suggested that the lack of OH effects in experiment 2 could be due to sex differences in the OH response, because women demonstrated larger OH effects during the $OH_{2℃}$ condition. Finally, exploratory analysis revealed that OA and OH effects were only weakly correlated.

5.2 STUDY II

5.2.1 Methods

In Study II, we investigated if it was possible to produce sensory attenuation of pain using self-induced, imagined self-induced, or other induced pressure pain. This was done using an algometer, a handheld device that is measuring pressure in kilopascal (kPa). In one condition, the experimenter pressed the algometer against the participant's thigh (other condition). In the second condition, the participant pressed the algometer against his/her own thigh (self condition). In the third condition, the experimenter pressed the algometer against the participant's thigh while the participants imagined that they pressed against their own thigh, holding an algometer that did not touch the participants body but were in proximity to the algometer handled by the experimenter (imagery condition; see figure 3). Pressure was increased by a steady rate of 50 kPa/s. Each condition was repeated three times. Participants were asked to signal when they experienced pain. Before the experiment, participants were trained to imagine that they pressed an algometer against their thigh without applying any real pressure to the algometer. The pain threshold of each condition, measured in kPa, were compared using mixed effects models.

Figure 3. The participant is imagining pressing the algometer on her thigh, while the experimenter pressed the algometer in the imagery condition.

5.2.2 Results

We found a significant difference between the self (521 kPa) and other (730 kPa) condition ($p < .001$). This means that the participants experienced the self-induced pressure as less painful (i.e., lower pain threshold) than the experimenter-induced pressure. There was also a significant difference between imagined self-induced pressure (619 kPa) and experimenter induced pressure ($p < .001$), as well as self-induced pressure ($p = .004$). There was no significant correlation between participants' rating of feeling of agency during the imagery condition and the imagery-induced pain attenuation.

5.3 STUDY III

5.3.1 Methods

Study III consisted of an extensive pre-registered QST protocol and an exploratory analysis of fMRI data collected when participants were exposed to tonic heat pain. The QST protocol included pressure pain threshold, heat pain threshold, heat tolerance, CPM, and temporal summation. During testing, participants rated their pain intensity with a NRS scale (0-10) on screen, using a trackball. Heat tolerance was defined as NRS 6/10 to avoid inducing excessive pain. CPM (see 4.6) was tested using ischemic pain, produced by a mechanical cuff around the participants' arm, as a conditioning stimulus. To induce ischemic pain participants were asked to flex their arm using a barbell until they rated the pain intensity in their arm as NRS 6/10. As a test stimulus, we measured the pressure pain threshold with an algometer, before and after the conditioning stimulus. The CPM effect (i.e., the difference between test stimulus pre vs. during conditioning stimulus) was compared between groups using a mixed effects model. Temporal summation (see 4.7) was measured using a pinprick stimulation on the left big toe. First, participants rated one pinprick stimulation. After 20 seconds, participants were given 15 pinprick stimulation at a rate of 1 Hz, that was rated continuously by the participant with the same procedure as CPM. The wind-up effect during the temporal summation protocol was estimated by comparing the first stimulation to the max rating during the 15 seconds of repeated stimulation. Comparison between groups were made using a mixed effects model. The fMRI data was collected while the participants were exposed to a heat stimulus, during 30 s, repeated three times. The temperature of the heat stimulus was calibrated to each individual's NRS 5/10 in pain intensity. Pain specific hemodynamic responses were compared between groups using an independent sample t-test.

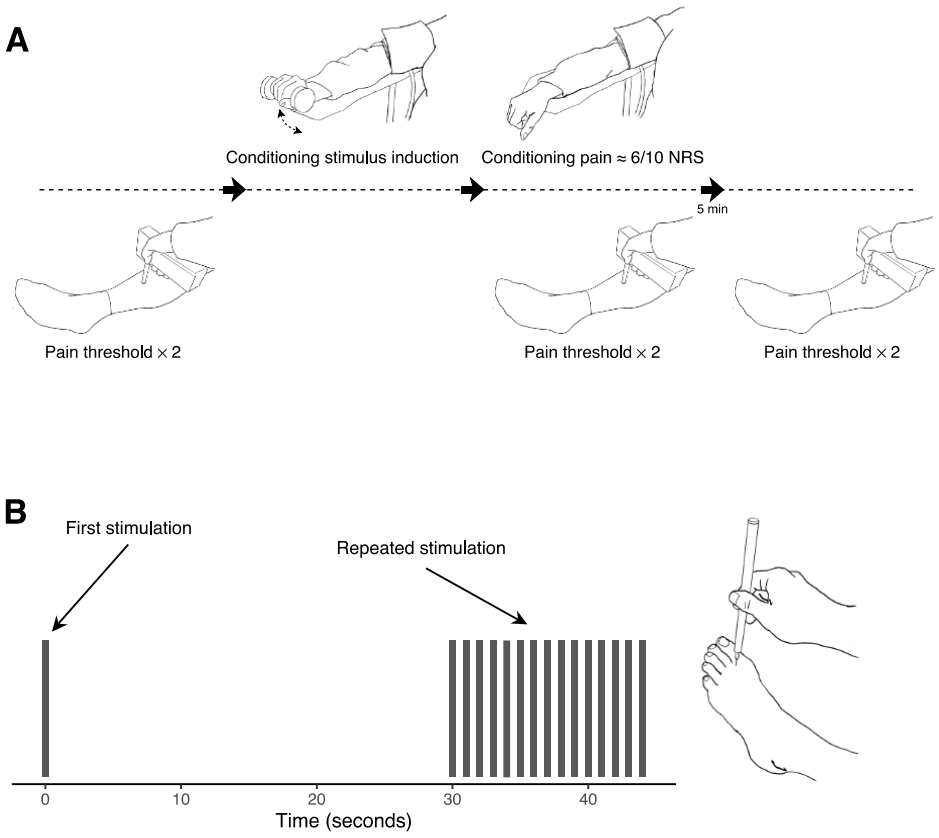

Figure 4. (A) Conditioned pain modulation procedure. (B) Temporal summation procedure.

5.3.2 Results

The NSSI group demonstrated higher pressure pain threshold and heat pain threshold, compared to the control group. But there was no difference between the groups regarding heat pain tolerance, which could be explained by ceiling effect in both groups (safety measure to avoid skin burns). The CPM effect was larger in the NSSI group than the control group. Estimated difference between the groups was 94 kPa. There was no difference in the wind-up effect measured by the temporal summation protocol. We found no correlation between pain testing outcomes (pressure pain threshold, heat pain threshold, CPM effect) and the frequency of, or duration of, NSSI behavior. Regarding the exploratory fMRI analysis, we found that the NSSI group, compared to the control group, displayed larger hemodynamic response in primary and secondary somatosensory cortex contralateral to the stimulation site. The difference between the groups was partly explained by the difference in the temperature between the groups during pain stimulation. The NSSI group also displayed larger hemodynamic responses in pain-related regions, measured with a machine-learning derived neural pain signature, based on independent data. But we found no difference between the groups regarding the stimulus-intensity independent pain signature. There was a significant correlation between the neural pain signature and the stimulus-intensity independent pain signature in the NSSI group, but not in the control group.

5.4 STUDY IV

5.4.1 Methods

In Study IV, we used a combined OA/OH protocol to measure pain modulation in 37 participants with ongoing NSSI and 39 healthy participants without NSSI. The procedure differed slightly from Study I (see 5.1). We included only three conditions: $OA_{2℃}$, $OH_{2℃}$, and control (see figure 5). All three conditions were repeated twice. Moreover, this time the procedure was combined with fMRI. Similar to Study I, we compared the experimental conditions ($OA_{2℃}$, $OH_{2℃}$) to the control condition, but the time interval of analysis changed slightly, based on the results of Study I, from the last 13 seconds to the last 12 seconds of T3. OA and OH effects, as well as group comparisons, were made using mixed effects models. The analysis of fMRI data was based on regions of interest, to increase statistical power. The analysis of OA was restricted to the brainstem, dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and thalamus. The analysis of OH was restricted to primary somatosensory cortex and secondary somatosensory cortex, insula, anterior cingulate cortex, and inferior frontal cortex. The hemodynamic response during OA and OH across groups was determined by contrasting OA with control and OH with control during the whole of T3. We also compared the effect of OA [OA-control] and OH [OH-control] between groups.

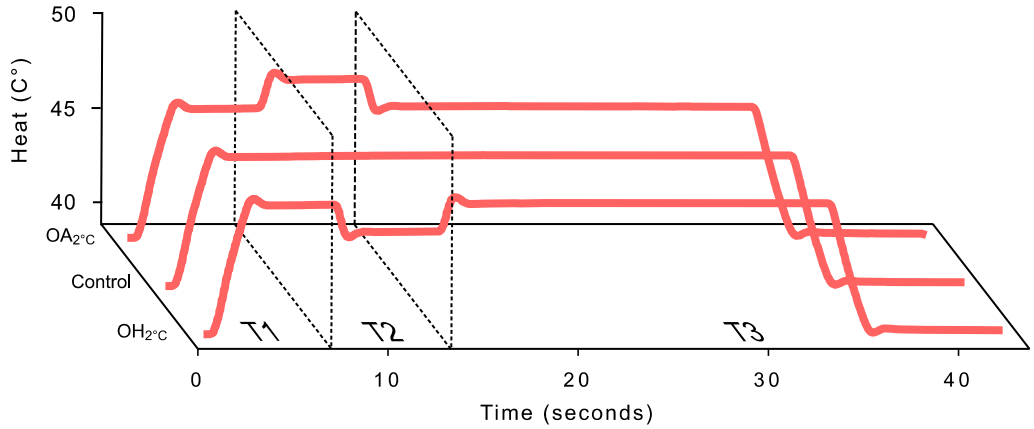

Figure 5. Mean heat stimulation (℃) during the different conditions of the OA/OH protocol in Study IV.

5.4.2 Results

Across participants, there was a significant OH response (NRS 0.39/10; $p < .001$) and OA response (NRS -0.89/10; $p = .001$). We also found that the NSSI group displayed lower OH response, compared to the control group. But there was no difference in OA responses between the groups. The OA and OH responses were weakly correlated ($r = 0.28$, $p = .012$). Regarding the fMRI data, we found a significant cluster of voxels in the primary somatosensory cortex related to the OH effect, across groups. But we found no other significant effects on the level of the brain, based on the regions of interest.

6 DISCUSSION AND CONCLUSIONS

To be able to understand the development and maintenance of NSSI behavior we should take the cost of pain into account. Due to the aversive nature of pain, self-harm behavior is more likely to persist if the behavioral cost of pain is reduced. Individuals with NSSI report feeling little or no pain while they self-harm. Even though there is evidence that intense emotional states, which are prevalent in the NSSI population, can affect the experience of pain, the reports of hypoalgesia are likely not explained solely by state-dependent factors. There is strong evidence from multiple laboratory studies that low pain sensitivity is a stable trait in individuals with NSSI. Nevertheless, the mechanisms behind hypoalgesia in individuals with NSSI are not known. Researchers have studied psychological factors, such as self-criticism and dissociative symptoms, and physiological factors, such as arousal and low levels of endogenous opioids, but there is still not enough evidence to explain the prevalence of state and trait-dependent hypoalgesia in the NSSI population. We have tried a new approach to study individuals with ongoing NSSI, using the same methods that have been used to study the mechanisms of pain modulation in individuals with long-term pain. Our general hypothesis was that trait-dependent hypoalgesia in the NSSI population could partly be explained by hyper-effective pain modulation. We have also assessed self-attenuation of pain, which could also contribute to hypoalgesia during self-injury.

6.1 EVIDENCE OF HYPER-EFFECTIVE PAIN MODULATION IN WOMEN WITH NSSI

The main findings of this thesis can be found in Study III and IV, which included tests measuring pain modulation and included both a group of women with ongoing NSSI and an age-matched control group of healthy women. Both studies suggest that women with NSSI have a hyper-effective pain modulation system. Women with NSSI downregulate pain to a greater extent (CPM in Study III) and upregulate pain to a lesser extent (OH in Study IV), compared to the women without NSSI. However, it is important to note that we cannot be sure that these differences in pain modulation can be attributed directly to NSSI for two reasons. First, the NSSI group was compared to a healthy population, not a psychiatric population, and thus, we do not know if the differences in pain modulation can be attributed to other psychiatric factors. For instance, hypoalgesia in the NSSI population has been attributed to general BPD symptomology (but even this theory was not supported by our data). Second, we did not find any correlations between the outcomes from the pain tests and the frequency and duration of NSSI. It is also important to point out that the NSSI group did not deviate from the control group on other pain tests measuring down-regulation of pain (OA in Study IV) and up-regulation of pain (temporal summation in Study III). We know that different measures of pain modulation do not correlate to a high degree (Kong et al., 2021; Nahman-Averbuch et al., 2014). By using multiple measures of both up- and downregulation we have identified aspects of the pain modulation system in the NSSI population that would be interesting to study further in the future.

6.2 SELF-ATTENUATION OF PAIN COULD PARTLY EXPLAIN LACK OF PAIN DURING NSSI

In Study II we found clear evidence that the pain threshold increases during self-induced pressure in a non-clinical sample. This result confirms earlier findings of self-attenuation of painful stimulation (Borhani, Beck, & Haggard, 2017, Braid & Cahusac, 2006). Self-

attenuation of pain could contribute to the low pain intensity reported by the NSSI population during self-injury. We also found that imagined self-administered pressure also raises the pain threshold, compared to experimenter-administered pressure, but not to the same extent as self-administered pressure. Imagery-induced self-attenuation has previously only been demonstrated regarding non-painful pressure. It is not clear if imagery-induced hypoalgesia have any relevance for explaining NSSI.

6.3 THE UTILITY OF A COMBINED OA/OH PROTOCOL

We have demonstrated the feasibility of using a combined OA/OH protocol on healthy participants and on a clinical group (i.e., women with NSSI). Apart from our two studies, OH has only been demonstrated once in the study by Alter et al. (2020), and never in a clinical sample or in combination with fMRI. The advantage of using a combined OA/OH protocol is that different aspects of pain modulation, both up- and downregulation of pain intensity, can be evaluated with an almost identical stimulation pattern. This means that you do not have to take confounding variables into account, such as stimulus modality, when studying inhibitory and facilitatory balance of pain modulation. Due to the low correlation between OA and OH, we know that OA and OH is measuring different aspects of pain modulation. The problem with OA and OH is that we do not really know what we are measuring. We know little of the underlying physiology of OA and OH. Furthermore, we do not know if the protocol is measuring something that is clinically relevant. However, in the case of OA, at least we know that patients with long-term pain tend to demonstrate reduced OA response (Szikszay et al., 2019). Based on the results of Study I, we decided to use ±2°C stimulus range, instead of ±1°C, which is traditionally used in OA protocols. This probably increased statistical power in Study IV. The downside with altering the stimulus range is that our results are not as easy to compare to other OA and OH studies that used the traditional stimulus range.

7 POINTS OF PERSPECTIVE

7.1 CLINICAL IMPLICATIONS

While there are no direct clinical implications of the studies in this thesis, I believe that these studies are valuable because they further our understanding of the role of pain in NSSI behavior. Study III and IV and this thesis suggests that previous reports of hypoalgesia in the NSSI population in observational and experimental studies, does not reflect respsone bias, but is rooted in how the nervous system modulates nociceptive signals. We still know little about pain modulation, but I believe that differences in pain modulation have its basis in genetic differences. If that is true, this means that the insensitivity to pain precedes NSSI behavior and could possibly be a risk factor for adolescents to engage and establish NSSI as a means to regulate emotions and signal distress. The genetic influence on hypoalgesia in the NSSI population could be studied with methods employed in behavioral genetics, such as twin studies and other family designs.

NSSI is difficult to treat. In a recent large scale randomized control trial (Simon et al., 2022), 18,882 outpatients with suicidal ideation were randomized to a care management intervention, skills training intervention, or treatment as usual. None of the interventions reduced the number of incidents of self-harm, compared to treatment as usual. Discouraging results like this suggests that we need to understand more about the function and maintenance of NSSI. The benefits and barriers model by Hooley and Franklin (2017) offers a new perspective on NSSI, in which the barriers to NSSI are central to understanding NSSI. Pain is probably one of the important barriers that stops many people from hurting themselves.

One way to incorporate pain in treatments of NSSI, is to try to normalize the sensitivity to pain in individuals with NSSI, or even increase the pain sensitivity. This seems to be the rationale in studies where individuals with NSSI have been treated with the naltrexone: an opioid antagonist that has been found to increase the sensitivity to pain in some studies (France et al., 2007). In a quantitative synthesis of studies of naltrexone treatment of self-injurious behavior in individuals with intellectual disabilities and autism, it was found that naltrexone reduced self-injurious behavior in 80% of the studies (Symons, Thompson, & Rodriguez, 2004). There are also a few studies in which BPD patients have been treated with naltrexone, with promising results, but these studies were small and lacked placebo-control (Roth, Ostroff, & Hoffman, 2006; Sonne et al., 1996). I think it would be interesting to conduct a placebo-controlled study of naltrexone, or another pharmacological intervention, to manipulate pain sensitivity in a psychiatric population in order to reduce NSSI behavior. However, it is important to note that even if hypoalgesia is an important factor in the etiology of NSSI—and that this trait could be manipulated with a pharmacological intervention—it does not mean that increasing pain sensitivity would decrease a behavior that is already established.

7.2 THE USE OF FMRI IN COGNITIVE NEUROSCIENCE

The reason why I have excluded imaging studies in the literature review of this thesis, and emphasized the behavioral results in our studies, instead of the fMRI results, is because during the years as a PhD student I have become skeptical of many experimental results that are produced using fMRI methods. I will try to justify my skepticism in a sort of addendum to this thesis. My criticism is based on what I characterize as the methodological problems and inferential problems in MRI-based cognitive neuroscience.

7.2.1 The methodological problems

In my opinion, the largest methodological problem in fMRI research is low statistical power which is expected to result in inflated effect sizes and publication of many false positive findings. A meta-analysis from 2011 estimated the median statistical power in human MRI studies to be 8% to detect estimated effect sizes (Button et al., 2011). In a later meta-analysis, the median statistical power to detect small effects ($d < 0.2$) was estimated to be 11% in cognitive neuroscience, 16% in psychology, and 16% in medicine (Szucs & Ioannidis, 2017). There is reason to believe that statistical power in cognitive neuroscience has increased slightly in years following the study by Button et al., (2011) because sample sizes in neuroimaging studies increase with about 0.74 participants each year (Szucs & Ioannidis, 2020). Still, most neuroimaging studies are very far from 80% power to a detect estimated effect size, which is often used by research funders, such as NIH, as a threshold for a study to be eligible for funding (Gelman, 2017). Given the low average power in these studies, significant results should be very uncommon in most subfields of cognitive neuroscience, but this is not the case (David et al., 2018; Fanelli, 2010). This implies that a lot of negative studies do not get published, and/or that questionable research practices often are used to turn negative results into positive results.

A common misunderstanding is that the risk of a significant result being a false positive is equal to the alpha level (usually 5%). This is not the case since the alpha level only represents the probability that the null hypothesis will be rejected given that the null is actually true. Instead, the risk that a finding is a false positive is called the false positive report probability, which can be estimated using a Bayesian model that accounts for the alpha level, the statistical power, and the prior probability of true finding (Wacholder et al., 2004). For example, if the probability of a true finding is 50% and the statistical power is 10%, given an alpha value of 5%, the risk of reporting a false positive finding is approximately 33%. Keep in mind that this estimate is based on the assumption that there is no bias involved. If the statistical model is modified in any way during analysis, for instance, by adding covariates, excluding outliers, or by changing timestamps and/or ROIs, or if you conduct multiple tests without proper correction of alpha, the risk of a false positive finding increases (see Simmons, Nelson, & Simonsohn, 2011). Unfortunately, these questionable research practices are common in the field of cognitive neuroscience (John, Loewenstein, & Prelec, 2012), which means that median false positive report probability is probably a lot higher than 33%. It is also important to note, that even if only one statistical model is constructed, but this model is influenced by the collected data in any way, the p-value cannot be taken at face value (Gelman & Loken, 2014).

If you take the low statistical power and the widespread analytical flexibility into account, you should not be surprised that results in cognitive neuroscience fail to replicate in pre-registered studies. The only large-scale multi-study replication of MRI results I know of was conducted by Boekel et al. (2015), who attempted to replicate the findings of studies which have reported correlations between structural MRI and behavior. Only one of the 17 findings was replicated, which resulted in a replication rate of 6%. But it is important to note that this study only included 38 participants, which was in some cases lower than the original studies.

So, what kind of sample size do we need to achieve acceptable statistical power in a fMRI study? Of course, sample size estimation varies depending on the effect that is studied and the design of the study, but there are very few effects in cognitive neuroscience that are estimated to be considered large (often defined as $d > 80$) (Poldrack et al., 2017), and in general, sample sizes need to reach hundreds, probably even thousands of participants to produce reproducible findings (Bossier et al., 2018; Turner et al., 2020). Based on the data

from the Adolescent Brain Cognitive Development Study (N = 11,878), fMRI studies need at least 2,000 participants to detect reproducible correlations between fMRI data and measurements outside the scanner (Marek et al., 2020). According to a recent preprint based on MRI data from UK biobank, even sample sizes of 100,000 participants is not enough to train predictive models that reliably detect depression (Schulz et al., 2022). Sample sizes at a large scale can only be achieved by organizing research consortiums. The UK biobank, Adolescent Brain Cognitive Development Study and ENIGMA Project are examples of this kind of collaboration between neuroscientists. Another solution is of course to compile data in meta-analyses, but these meta-analyses are unfortunately affected by bias in the literature (Ioannidis, 2008).

7.2.2 The inferential problems

The inferential problems in cognitive neuroscience are more subtle, but I would argue, even more serious than the methodological problems. I claim that the term cognitive neuroscience is often a misnomer when it comes to fMRI research, because (1) cognitive theories are seldom tested in fMRI studies and (2) it is very hard to test cognitive theories using fMRI methodology.

Tressoldi et al. (2012) compiled 199 fMRI studies concerning mental functions published in high impact journals between 2007-2011. Out of these 199 studies, only 20 studies aimed to actually test cognitive theories. The aim of the other 179 studies was instead anatomical localization of cognitive functions. In 2013, the journal *Perspectives on Psychological Science* had a special section about how functional neuroimaging can inform cognitive theories. It is telling that many of the contributions to this section did not even try to answer the question about how fMRI can inform cognitive theories, but instead discussed research based on anatomical localization (Coltheart, 2013). For example, the pain researchers Wager and Atlas (2013) state that it is important that psychological theories are informed and constrained by brain evidence, but the authors do not give even one example of how this has been done or could be done in the field of pain research (Coltheart, 2013).

Anatomical localization does not give us information about cognitive processes in the brain. It is important to make a distinction between explanations at the level of the brain and at the level of cognition—a distinction between the biological properties of the brain and the information processes of the brain. We know that information processes emerge due to a set of biological properties of the brain, but we do not know how. For example, we still understand little of the causal relation between the nervous system and the behavior of the small worm C. elegans, even though neuroscientists have extensively characterized the 302 neurons of the species (Niv, 2021). Moreover, we do not even understand the information processes in artificial neural networks used in deep learning, even though we have created them ourselves and can measure all the synaptic weights in the network, which is not possible when studying biological neural networks (Hiesinger, 2021). If we cannot understand the nervous system of simple organisms, such as C. elegans, or the neural networks we have created ourselves, we are very far from understanding the human brain.

The brain is a complex network of 100 billion neurons. Each neuron may be connected to 10,000 other neurons, which means that the number of synapses in the brain could be as many as 1000 trillion (10^{21}) (Zhang, 2019). This level of complexity can make it conceptually or computationally impossible to detect causal relations between variables, independent of the amount of data (Glymour & Sanchez-Romero, 2018). Even if we could register the activity in every neuron, it still would be very hard to understand how the brain computes

information. This suggests that it is not likely that fMRI, an indirect measure of neuronal activity in voxels, each containing up to several millions of neurons, will not contribute very much to the understanding of how such a complex system achieves computations.

Another reason why we know very little of the relation between the brain and cognition is because the vehicle of representations often does not share features with the content of representations (Millikan, 1991). For example, the word "blue" is not colored blue, and the representation of blue in the brain is not colored blue or shaped in the letters "b-l-u-e". The failure to take the content/vehicle distinction into account is most obvious in the understanding of modularity in cognitive neuroscience. Many cognitive scientists believe that the brain is characterized by cognitive modularity—that the brain consists of information processing subsystems that have specialized functions (Barrett & Kurzban, 2006). But this does not mean that the brain is characterized by anatomical modularity—that each cognitive subsystem can be localized in a specific region or a network of regions in the brain, measured by voxels or voxel-based clusters, which seems to be the justification for anatomical localization studies. In fact, the small effect sizes and high inter- and intra-individual variability in fMRI studies (Elliot et al., 2020; Seghier & Price, 2018) suggest that this is not the case. Of course, I am not denying that there are regions and networks that are slightly more involved in specific tasks, but that does not mean that anatomical localization explains anything on a cognitive level. It should be humbling to realize that it is not possible to understand the software of a computer by measuring electrical activity in the hardware or by creating "lesions" by removing transistors from the microprocessor of the computer (Jonas & Kording, 2017). To be fair, the idea that simply measuring biological variables somehow provides us with a deeper understanding of complex biological systems is not limited to cognitive neuroscience. For example, the biologist Yuri Lazebnik (2002) has argued that a biologist would not be able to even fix a radio, using the methods of experimental biology.

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