Just a touch away

CT-optimal touch perception and its influence on pain and itch

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De beleving van CT-optimale aanraking en de invloed ervan op pijn en jeuk
(met een samenvatting in het Nederlands)

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Larissa Lauren Meijer

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Promotoren:
Prof. dr. H.C. Dijkerman
Prof. dr. M.J. van der Smagt

Copromotor:
Dr. C. Ruis

Beoordelingscommissie:
Prof. dr. R. Ackerley
Prof. dr. R. Geenen
Prof. dr. L. Kenemans
Dr. I. Morrison
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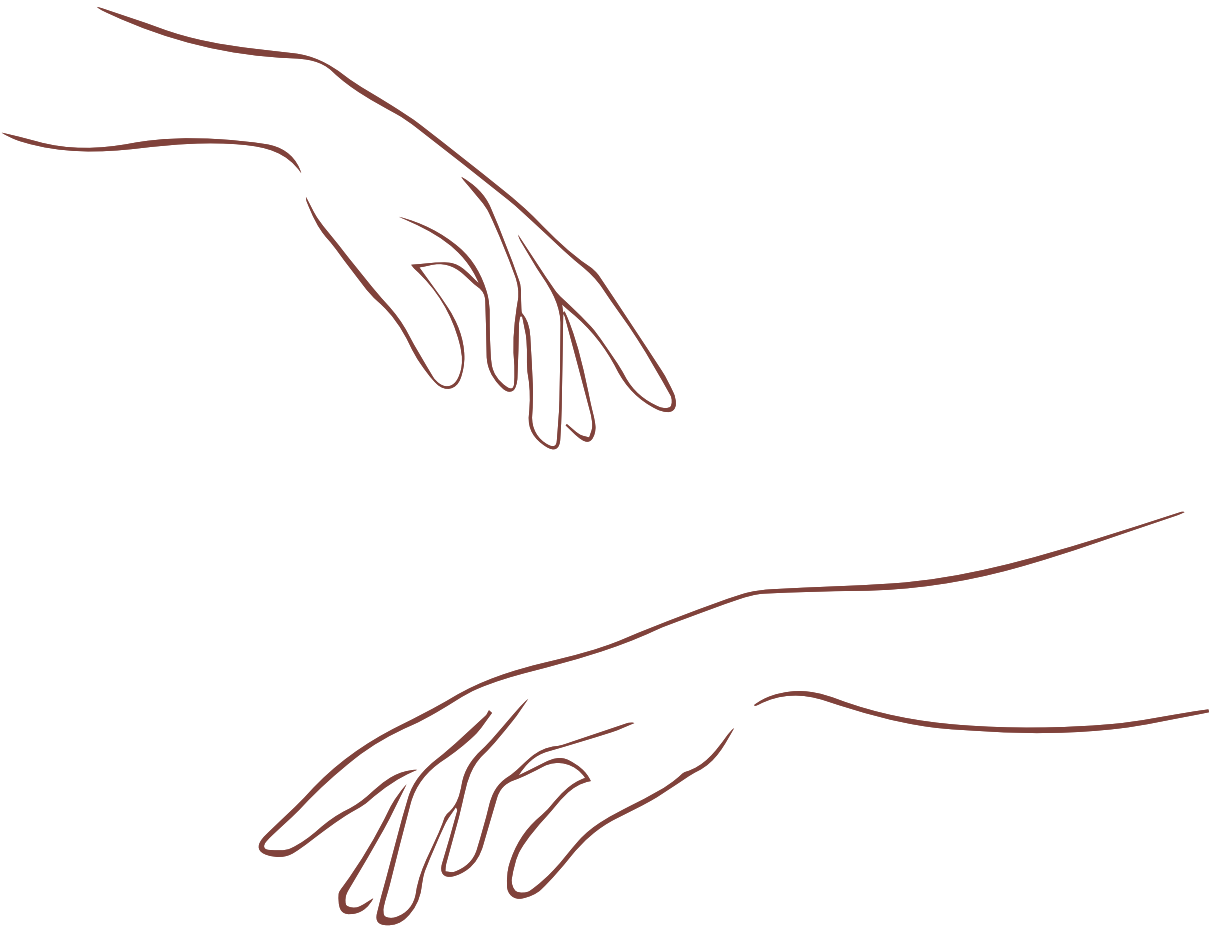
Contents

Chapter 1



General Introduction

"...Reaching out for something to hold,
Looking for a love where the climate is cold..."
Hall & Oates, Out of Touch, 1984.

1.1. CT-optimal touch and affective touch

Touch is one of our senses and it is the first to develop in the fetus (Fagard et al., 2018). This already shows how vital the ability to perceive touch is. Touch is important to discriminate, localize and identify stimuli that make contact with our skin. It was therefore thought that the sense of touch had a merely discriminative role. The discriminative function of touch appears to be subserved mainly by the large myelinated Aβ-fibers which project to the primary somatosensory cortex (McGlone et al., 2014). However, twenty to thirty years ago research in humans started to focus on a different type of fiber involved in the processing of touch. It was already known that non-human mammals have a particular type of low-threshold unmyelinated fibers which transmit tactile input: the C-tactile (CT) – fibers (Olausson et al., 2010). The CT-fibers are present in the hairy skin, it was therefore thought that humans had lost this seemingly more primitive system during evolution together with the loss of most of our bodily hair. However, since 1990 we know that humans do possess the CT-fibers and since then research has focused on investigating the processing of the CT-fibers and its properties (Nordin, 1990).

The CT-fibers respond to gentle slow stroking of the hairy skin. The optimal stroking velocity is 3 cm/s with a range of 1 – 10 cm/s (Olausson et al., 2010). When activating the CT-fibers, by gently stroking the skin at optimal velocity, a pleasant sensation is elicited. CT-optimal touch is therefore related to perceived tactile pleasantness (Vallbo et al., 2009). Based on the relationship between CT-optimal touch and tactile pleasantness, Vallbo et al. (2009) introduced the *affective touch hypothesis*, which states that 'the essential role of the CT-system is to convey affective aspects of light touch'. Therefore, CT-optimal touch is also referred to as affective touch. Research shows that CT-optimal touch can be applied by a soft brush, but the CT-fibers respond most vigorously to stimuli with a temperature of around 34°, i.e. skin temperature (Ackerley, Backlund Wasling, et al., 2014). Therefore, it is most effective to apply CT-optimal touch with the hand. When activated, the CT-fibers transmit signals to the dorsal horn of the spinal cord and from thereon to several brain regions of which the insula appears to be a key region (McGlone et al., 2014, see Figure 1.1). As the insula has interoceptive properties and is linked to the hedonic values of somatosensory senses i.e. touch, pain and itch (Craig, 2009), its activation is also linked to the perceived pleasantness of CT-optimal touch (Gordon et al., 2013).

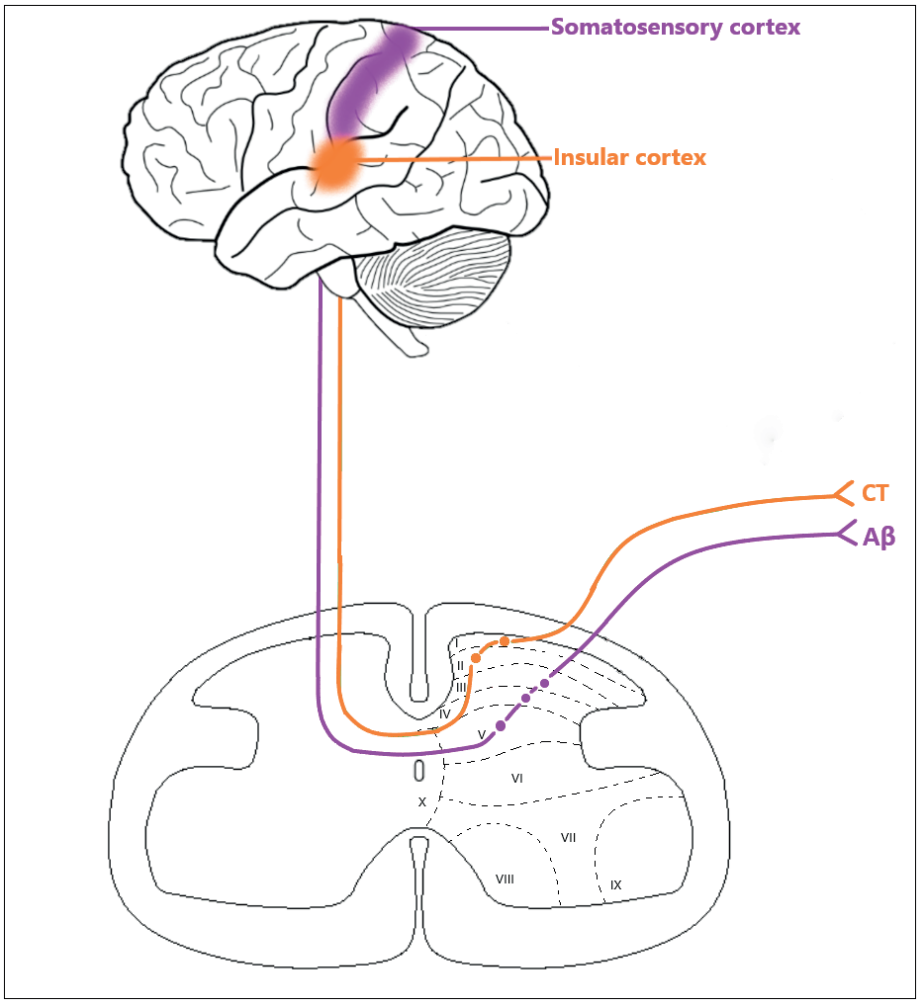


Figure 1.1. Visualization of the discriminative touch system (Aβ fibers) and the CT-system

1.2. CT-optimal touch, acute pain and itch

Apart from the CT-fibers, there are also other unmyelinated C-fibers not related to touch. These C-fibers mediate two other somatosensations: pain (Vogt & Sikes, 2000) and itch (Schmelz et al., 1997). When looking into the neurophysiology of the CT- and C-fibers, signals from both fibers are transmitted to laminae I and II of the dorsal horn of the spinal cord and from thereon to several regions including the insula and ACC (Bell, 2018; McGlone et al., 2014; Wallengren, 2005). Based on this overlap in (supra)spinal processing, these somatosensations might interact

with one another. Indeed, painful stimuli can interact with the processing of itch at the dorsal horn of the spinal cord. Here, C-fibers transmitting pain inhibit C-fibers involved in itch processing thereby preventing further transmission of the itch stimuli (Davidson & Giesler, 2010). This is behaviorally observed when scratching the itchy skin. So, we know that pain and itch are processed by the C-fibers, that there is a connection between these two sensations at the dorsal horn of the spinal cord and that the insula and ACC are highly involved. Importantly, as described, the processing of the CT-fibers relies on similar (supra)spinal regions. As current treatments for itch and pain are often insufficient (Bicket & Mao, 2015; Fowler & Yosipovitch, 2019), it is of importance to investigate whether CT-optimal touch can influence itch and pain as well. Currently, there are some studies on the interaction between CT-optimal touch and acute pain. These studies show that CT-optimal touch can reduce acute pain experience in healthy individuals (Gursul et al., 2018; Habig et al., 2017; Krahé et al., 2016; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018). Based on these studies, we introduce a novel model on the underlying mechanism of CT-optimal touch and its interaction with pain, which will be discussed in **chapter 2**. We hypothesize that there is a relationship between CT-optimal touch, pain and itch. If so, one could argue that CT-optimal touch is one of the somatosensations influencing and interacting with the other two; pain and itch (see Figure 1.2).

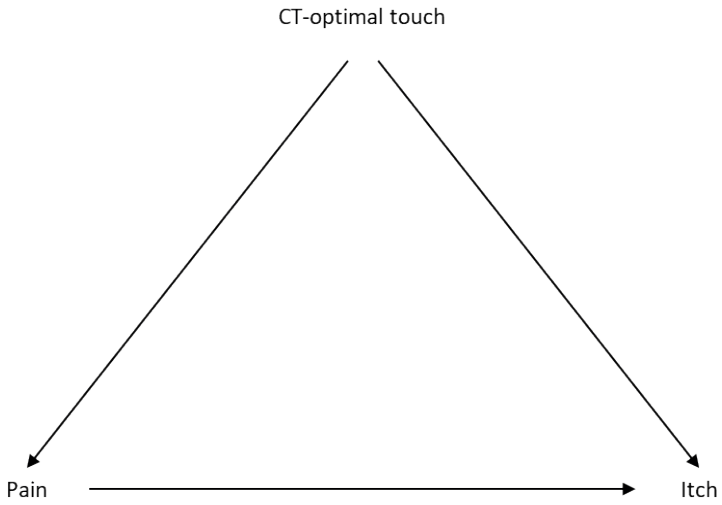


Figure 1.2. Visualization of the proposed interaction between CT-optimal touch, pain and itch

1.3. CT-optimal touch and chronic pain

Chronic pain is defined as ongoing disabling pain which overstays the natural healing time and must be present for at least three months (Świeboda et al., 2013). Currently, 1 out of 5 people suffer from chronic pain worldwide and this prevalence increases significantly in elderly (Zimmer et al., 2022). As people live longer, the prevalence of age-related diseases will increase as well. An example of this are neurodegenerative diseases of which Parkinson's Disease (PD) is the second-most common after Alzheimer's Disease (Edinoff et al., 2020). In PD 30-85% suffers from chronic pain, a highly undertreated and underdiagnosed non-motor symptom (Edinoff et al., 2020). This highlights the importance of finding a suitable treatment for this highly disabling symptom (Marques & Brefel-Courbon, 2021). Currently, treatment of chronic pain relies on a multimodal approach in which pharmacological, non-pharmacological and physical rehabilitation are combined, but still appears insufficient (Bicket & Mao, 2015). The underlying neural mechanisms causing chronic pain are not fully understood yet. However, in most chronic pain subtypes the insula, ACC and prefrontal cortex show structural and functional changes (Kuner & Flor, 2016). As these regions are also highly involved in the processing of CT-optimal touch and CT-optimal touch ameliorates acute pain, one could argue that CT-optimal touch might influence chronic pain as well.

Interestingly, a recent study of Di Lernia et al. (2020) shows that CT-optimal touch can reduce pain experience in chronic pain patients compared to touch vibration. Even though this is the first study showing that CT-optimal touch can also reduce chronic pain in a patient group, it was performed in a lab setting. To investigate whether it is feasible to use CT-optimal touch as a new non-pharmacological treatment for chronic pain, the next step will be to use CT-optimal touch in a home-setting. Furthermore, as the CT-fibers respond most vigorously to stimuli with body temperature and the study of von Mohr, Krahé, et al. (2018) shows that the effect of CT-optimal touch on acute pain is larger when a romantic partner provides touch, it is important to implement skin-to-skin contact by the partner as well.

As described previously, many PD patients suffer from chronic pain and a sufficient treatment is lacking. Chronic pain in PD seems to be caused by overactivation of regions involved in the motivational aspects of pain i.e. the insula and ACC (Antonini et al., 2018; Tseng & Lin, 2017). As these regions are also involved in CT-optimal touch and seem to play a role in the pain ameliorating function of the CT-system, PD patients suffering from chronic pain could benefit from CT-optimal touch. Therefore, within this thesis I will focus on this particular patient group.

As much is still unknown regarding the relieving effect CT-optimal touch appears to have on chronic pain, it is necessary to investigate which factors influence this effect. One of these factors might be tactile attention. Touch automatically draws attention towards the stimulated area (Chapman, 2009). In addition, previous research shows that attention can serve as a pain distractor (Bascour-Sandoval et al., 2019). We will therefore study if tactile attention can influence pain experience. Another factor might be touch application site. It is currently unknown if there is any difference in effectiveness between applying CT-optimal touch directly at the pain location or at a different bodily location. Therefore, we will compare applying CT-optimal touch ipsilaterally to pain stimulation as well as contralaterally. Inducing chronic pain in a lab is, besides being unethical, almost impossible as it needs to be present for longer than three months to be defined as chronic pain (Świeboda et al., 2013). However, it is possible to induce temporal summation of second pain (TSSP), also referred to as wind-up pain, which relies on activating the nociceptive C-fibers (Fidanza et al., 2021). By repetitively stimulating these fibers a burning and/or tingling sensation can be elicited (Staud et al., 2007). TSSP seems to reflect central sensitization, a process linked to several chronic pain conditions and could therefore serve as a model for chronic pain in healthy individuals. A recent study of Fidanza et al. (2021) investigated the effect of CT-optimal touch on TSSP. This study shows that CT-optimal touch effectively reduced TSSP compared to a very slow type of touch with a velocity of 0.3 cm/s and a no touch condition. However, here they only provided touch on the same body part as where pain was induced. If CT-optimal touch can reduce chronic pain and we eventually want to use it as a treatment, it is important to know whether touch should be applied at the pain location or that touch- and pain location can be different. Therefore, in **chapter 6** we investigated the effect of CT-optimal touch on TSSP, using the same paradigm as Fidanza et al. (2021). In addition, we also investigated if tapping the skin, used as a form of tactile attention, reduced TSSP and compared ipsilateral and contralateral touch application. This will provide further information on the possibility to use CT-optimal touch as a generalized treatment for chronic pain.

1.4. CT-optimal touch perception and touch deprivation

In addition to the possible interaction of CT-optimal touch on chronic pain and itch, in this thesis CT-optimal touch perception when experiencing touch deprivation is discussed. Touch deprivation is defined as a significant discrepancy between touch frequency and touch wish (Beßler et al., 2020). As mentioned, gentle slow stroking of the skin can elicit a pleasant sensation and is therefore also referred to as affective touch. In addition to the top-down regulated hedonic value of CT-optimal touch, other top-down processes seem to play a role as well (Craig, 2009). Social factors such as the relationship between the touch receiver and touch provider and contextual factors such as positive expectations towards touch influence if CT-optimal touch is perceived as pleasant (McGlone et al., 2014). In addition, these social factors not only influence the perceived pleasantness but also the beneficial properties of CT-optimal touch. Research shows that when CT-optimal touch is provided by a romantic partner there is stronger pain reduction compared to touch provided by an experimenter (von Mohr, Krahé, et al., 2018). As CT-optimal touch contains such a strong social component, the perception of CT-optimal touch might also be influenced by how often we receive social, affective touch.

Indeed, a study of Sailer and Ackerley (2019) shows that frequency of touch influences the perception of CT-optimal touch. CT-optimal touch is perceived as less pleasant when adults receive interpersonal touch infrequently. However, in this study 80% of the participants who received touch infrequently reported to have no partner and/or children while 28% of the control group did. Therefore, it could be that participants were feeling touch deprived due to a limited social network. This limits the generalizability of this study. To generalize these results to society, a large group of people should experience touch deprivation.

To contain the spread of the COVID-19 virus a variety of restrictions were implemented such as social distancing, isolation and quarantine (Verity et al., 2020), all resulting in a limitation of physical and social interactions. Even though this affected many people in different ways, it also provided the opportunity to investigate in a large community sample whether people were experiencing touch deprivation and if this affected our perception of CT-optimal touch. These research questions will also be discussed in the current thesis.

1.5. Thesis outline

In the previous sections I provided an overview of the current knowledge of CT-optimal touch. Based on this knowledge we designed a novel model on the underlying mechanisms of CT-optimal touch and acute pain and the interaction between these two somatosensations, this will be discussed in **chapter 2**. This novel model is the foundation of this thesis and is incorporated in the designed studies. Within this thesis the following research questions will be answered:

1. Can CT-optimal touch reduce electrically induced itch experience? In the study discussed in **chapter 3**, participants received electrically induced itch while simultaneously receiving CT-optimal touch and CT non-optimal touch. This study shows that CT-optimal touch effectively reduced itch. Interestingly, this effect was independent of the perceived pleasantness of CT-optimal touch.

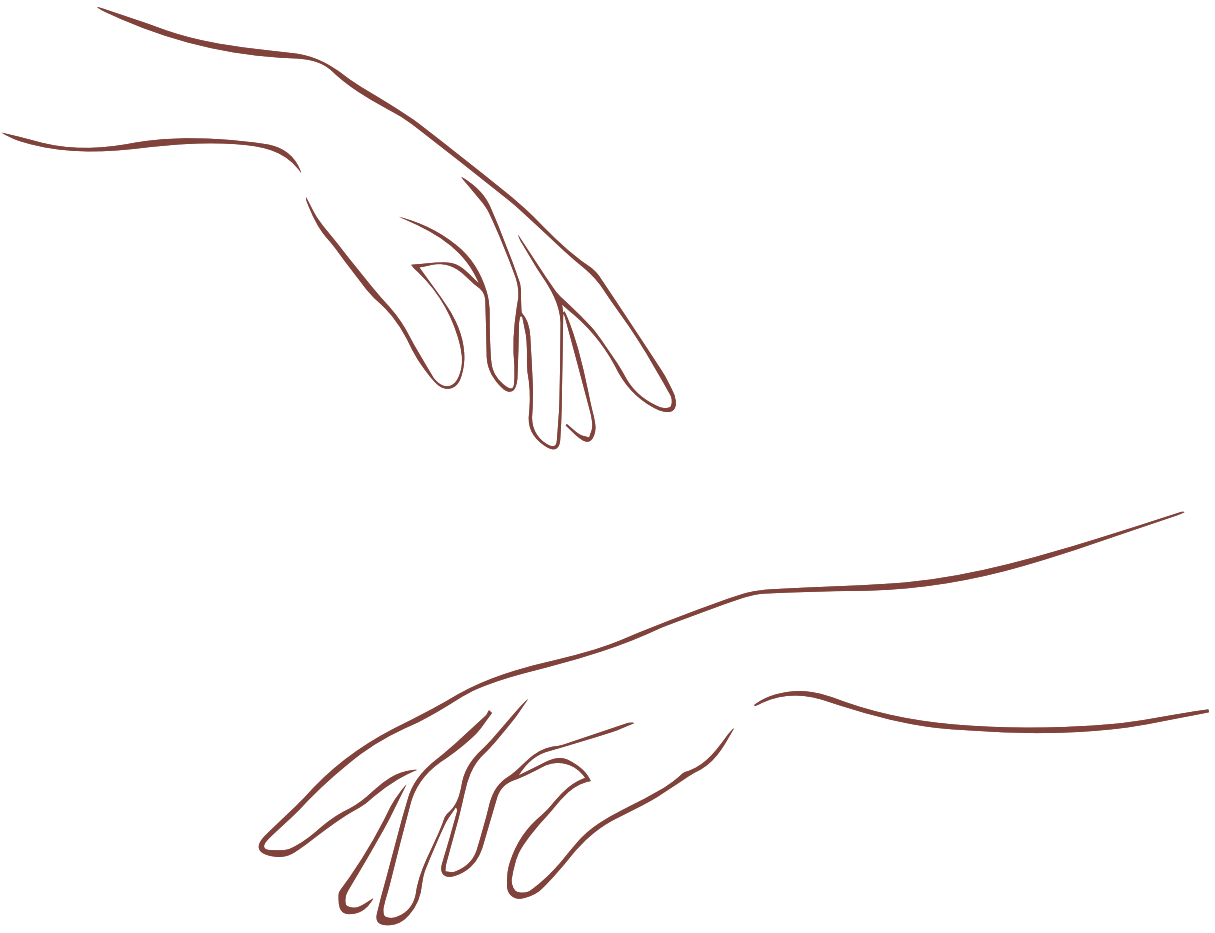
2. Can CT-optimal touch reduce chronic pain experience? In **chapter 4** and **chapter 5** a longitudinal study on the effect of CT-optimal touch on chronic pain in Parkinson's patients is presented. In **chapter 4** a unique case report of one of the participants of the larger study is described. Here, the participant's pain fully diminished after receiving CT-optimal touch for two days. Interestingly, this effect persisted even after CT-optimal touch administration had stopped. This has not been reported yet and the results were clearly different from the other participants in this study. As such, the single case report is discussed separately in **chapter 4** and the other participants are described, as a total sample, in **chapter 5**. **Chapter 5** focuses on the longitudinal study and data analysis on the whole sample. Here, CT-optimal touch has an immediate relieving effect on chronic pain. This effect is independent of the perceived pleasantness of CT-optimal touch.

3. Does the pain ameliorating effect of CT-optimal touch depend on tactile attentional effects and touch application site? **Chapter 6** contains an experimental study in which the effect of CT-optimal touch on temporal summation of second pain (TSSP) is investigated. TSSP or wind-up pain activates the C-nociceptors which can elicit a burning and/or tingling sensations. This is linked to central neuronal sensitization, a process related to chronic pain (Staud et al., 2007). While TSSP was induced, participants received on the contralateral and ipsilateral side CT-optimal touch, CT non-optimal touch or a Tapping condition. The Tapping condition was used as a control condition for spatial tactile attention. This study showed that spatial tactile

attention alone cannot reduce TSSP. Furthermore, CT-optimal touch can reduce TSSP and this effect appeared independent of touch application site. This effect in general was also independent of perceived pleasantness.

4. Is CT-optimal touch perception influenced by touch deprivation? This question will be answered in **chapter 7**. Here, a large online community sample study is described in which CT-optimal touch perception and touch deprivation were measured. This study shows that during the COVID-19 pandemic participants felt touch deprived. Furthermore, feeling touch deprived is related to increased perceived pleasantness of observing touch.

Chapter 2



Neural basis of affective touch and pain; A novel model suggests possible targets for pain amelioration

Larissa L. Meijer
Carla Ruis
Maarten J. van der Smagt
Erik J. A. Scherder
H. Chris Dijkerman

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Abstract

Pain is one of the most common health problems and has a severe impact on quality of life. Yet, a suitable and efficient treatment is still not available for all patient populations suffering from pain. Interestingly, recent research shows that low threshold mechanosensory C-tactile (CT) fibres have a modulatory influence on pain. CT-fibres are activated by slow gentle stroking of the hairy skin, providing a pleasant sensation. Consequently, slow gentle stroking is known as affective touch. Currently, a clear overview of the way affective touch modulates pain, at a neural level, is missing. This review aims to present such an overview. To explain the interaction between affective touch and pain, first the neural basis of the affective touch system and the neural processing of pain will be described. To clarify these systems, a schematic illustration will be provided in every section. Hereafter, a novel model of interactions between affective touch and pain systems will be introduced. Finally, since affective touch might be suitable as a new treatment for chronic pain, possible clinical implications will be discussed.

2.1. Introduction

Pain is a fascinating phenomenon; it can be the friend that protects us from harm, but it can also be the enemy that makes us suffer. For this reason, pain has been studied extensively over the last century. We now have substantial knowledge about the neural processing of pain (Bourne et al., 2014). Unfortunately, many people still suffer from (chronic) pain. In the United States approximately 19 – 43% of the adult population suffers from chronic pain (classified as, when pain lasts longer than 3 months) (Pitcher et al., 2019), in the UK 33 – 50% (Fayaz et al., 2016) and in Latin-American, Asian and African countries the incidence of chronic pain is estimated between 13 and 51% (Sá et al., 2019). These statistics underline the fact that chronic pain is a major health problem. Chronic pain severely impacts mental health, leading to conditions such as depression, anxiety, anhedonia, and impacts quality of life in general (Hylands-White et al., 2017; Simons et al., 2014). In addition, the prevalence of painful conditions, for example osteoarthritis and lower back pain, might increase with aging and since the general population is getting older, more people will suffer from chronic pain in the near future (Schwan et al., 2019). All these factors highlight the importance of finding new ways to reduce pain.

Interestingly, recent research suggests that affective touch might be a possible candidate for pain amelioration. Affective touch is gentle stroking of the skin which provides a pleasant sensation (Björnsdotter et al., 2010). This type of touch activates a particular type of low threshold mechanosensory C-fibres (C-tactile or CT-afferents), which appear to modulate pain (Liljencrantz et al., 2017). CT-afferents can be activated by slow stroking with a soft brush or with the hand, between 1 and 10 cm/s (optimal activation at 3 cm/s), and is therefore also referred to as CT-optimal touch (Björnsdotter et al., 2010). Recent behavioural and neurophysiological research confirms that the CT-afferent system and pain are connected. CT-optimal touch appears to be effective in reducing acute pain (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018). This finding makes CT-optimal touch a promising candidate for a new pain intervention, which could be especially helpful for people suffering from chronic pain conditions as adequate treatments are lacking.

A clear overview of the neural mechanisms that could be involved in the modulatory effects of CT-optimal touch on pain is missing in the present literature. This review aims to resolve this gap by describing the neural basis of the CT-afferent system, an overview of the pain system, and the neural interaction between these two somatosensory modalities. As CT-optimal touch might be a promising candidate to reduce chronic pain, we will subsequently

discuss the possible interaction between CT-optimal touch and chronic pain. In addition, clinical implications for chronic pain reduction will be discussed.

2.2. The neurophysiology of affective touch and pain

2.2.1 Affective touch/CT-optimal touch

The skin is our largest organ and helps us to engage with the world. It is innervated by three types of sensory nerve fibres, A-Beta (Aβ), A-Delta (Aδ) and C-fibres, which mediate our somatosensations (Zimmerman et al., 2014). Historically, tactile sensibility (touch) was thought to be signalled exclusively through fast conducting (50 m/s) myelinated Aβ-fibres. Aβ-fibres have a high spatial and temporal resolution and are linked to the discriminative aspects of touch (McGlone et al., 2014).

In contrast, affective touch concerns the more affective and pleasant aspects of touch and activates a subgroup of C-fibres known as C-tactile (CT) fibres (Björnsdotter et al., 2010). CT-fibres are unmyelinated slow conducting afferents and have a low temporal and spatial resolution (Vallbo et al., 1999). The CT-afferents respond to innocuous stimuli such as slow stroking of the hairy skin (most effectively between 1 and 10 cm/s, optimal speed is 3 cm/s), which can be applied with a soft brush or hand (Ackerley, Carlsson, et al., 2014; Olausson et al., 2010). Moreover, the CT-system responds most vigorously to tactile stimuli that are around 34˚C, that is skin temperature (Ackerley et al., 2018). As an optimal stroking speed of 3 cm/s is required to activate the CT-fibres, this type of touch is also referred to as CT-optimal touch. Since this review simply focuses on the underlying mechanisms of affective touch, rather than the perceived pleasantness and social component, the term CT-optimal touch will be used from hereon.

Recent research has focused on the underlying neural pathway of the CT-fibres. As this has already been described thoroughly in a state of the art review of McGlone et al. (2014), only a short overview and more recent insights will be provided here. A schematic overview of the CT-system is shown in Figure 2.1.

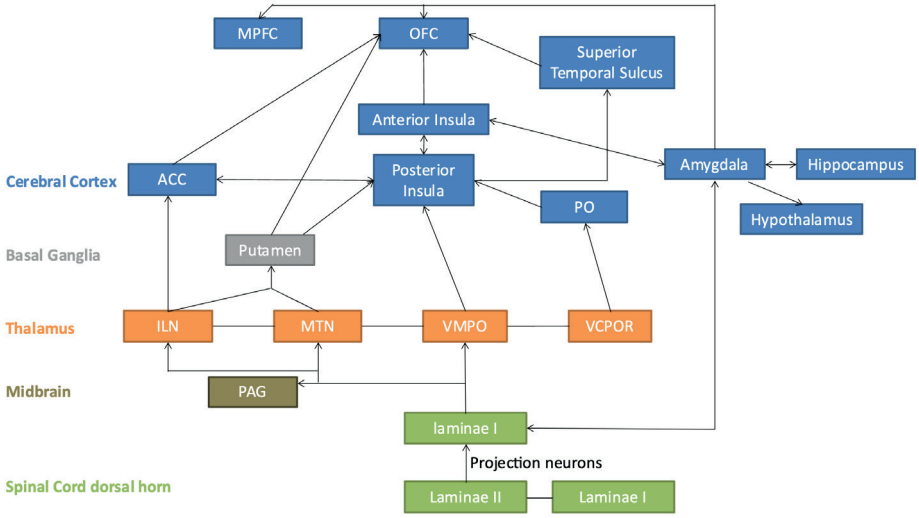

Figure 2.1. Schematic overview of neuronal projections of the CT-afferent system
PAG=periaqueductal Grey; ILN= intralaminar thalamic nuclei; MTN= medial thalamic nuclei; VMPO= ventral medial posterior thalamic nuclei; VCPOR= ventral caudal portae thalamic nuclei; PO= parietal operculum; ACC= anterior cingulate cortex; OFC= orbitofrontal cortex; MPFC= medial prefrontal cortex. This figure is based on the following literature: Beauchamp et al. (2008); Craig (2002, 2009); Craig et al. (2000); Gordon et al. (2013); Marshall and McGlone (2020); I. Morrison (2016); Olausson et al. (2008); Sailer et al. (2016).

The CT-fibres transmit signals to the superficial laminae I and II of the spinal cord dorsal horn; from thereon the signal is conveyed to several medial and intralaminar thalamic nuclei. It is thought that transmission occurs through the spinothalamic tract (STT) (McGlone et al., 2014). However, recent research shows that spinothalamic ablation does not affect the CT-system, suggesting that the CT-afferents possibly project through the dorsal column of the spinal cord to the thalamic nuclei (Marshall et al., 2019). Furthermore, animal research suggests that CT-afferents access the dorsal column through an interneuronal zone between laminae II and V (Abraira et al., 2017). However, it is currently not completely clear how the CT-afferents are projected to the thalamus, but multiple ascending pathways may be involved (Marshall & McGlone, 2020). At a cortical level, several regions are activated, starting with the posterior insula and, from there, the anterior insula, anterior cingulate cortex (ACC), superior temporal sulcus, orbitofrontal cortex (OFC), medial prefrontal cortex (MPFC), amygdala, hippocampus and hypothalamus are activated (Figure 2.1: Beauchamp et al., 2008; Craig, 2002, 2009; Gordon et al., 2013; I. Morrison, 2016; Sailer et al., 2016). As mentioned, the CT-system is linked to the affective experience of touch. The activation of especially the insula and ACC account

for this affective component (Gordon et al., 2013). In addition, the OFC and MPFC are linked to our (social) reward system, which supports their function in the affective (rewarding) aspects of this type of touch (Gordon et al., 2013; von Mohr, Crowley, et al., 2018).

2.2.2 Pain

Pain is defined as 'a complex sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (International Association for the Study of Pain: Bell, 2018). Pain can be divided into acute and chronic pain. Acute pain is regarded as a normal reaction to a harmful stimulus. Acute pain warns us that something is wrong and therefore plays a necessary and protective role. When pain exceeds its normally stated healing time and is present for at least 3 months, it is classified as chronic pain (Świeboda et al., 2013). Chronic pain is seen as a disease on its own and has a severe impact on quality of life, affecting physical and mental functioning (Anwar, 2016).

The neural mechanisms underlying acute pain have already been described in reviews by Bell (2018) and Hudspith (2016). Therefore, only a short overview and schematic illustration will be presented. Painful or noxious stimuli are transmitted by Aβ-, Aδ- and C-fibres to the dorsal horn of the spinal cord. From here, a distinction between the lateral- and medial pain system can be made, illustrated in Figure 2.2.

The Aβ- and Aδ-fibres project through the STT to the ventral thalamic nuclei and are part of the lateral pain system. These thalamic nuclei project directly to the secondary somatosensory cortex (S2), the primary somatosensory cortex (S1), insula and parietal operculum (PO) (Apkarian et al., 2005; Lenz et al., 2004; Peyron et al., 2000; Scherder et al., 2003). This system carries information about the sensory-discriminative aspects of pain (Woller et al., 2017).

The C-fibres, on the other hand, project through the STT to the medial and intralaminar thalamic nuclei and are part of the medial pain system. This system carries information about the motivational-affective aspects of pain (Scherder et al., 2003; Sewards & Sewards, 2002; Vogt & Sikes, 2000). Through the thalamic nuclei the posterior insula, anterior insula, ACC, S2, PO, amygdala and OFC are innervated (Garcia-Larrea & Peyron, 2013; Lu et al., 2016; Peyron et al., 2000; Schweinhardt & Bushnell, 2010). Especially the anterior insula and the ACC appear necessary for the affective components of pain (Apkarian et al., 2005; Lu et al., 2016; Peyron et al., 2000; Sewards & Sewards, 2002; Vogt & Sikes, 2000).

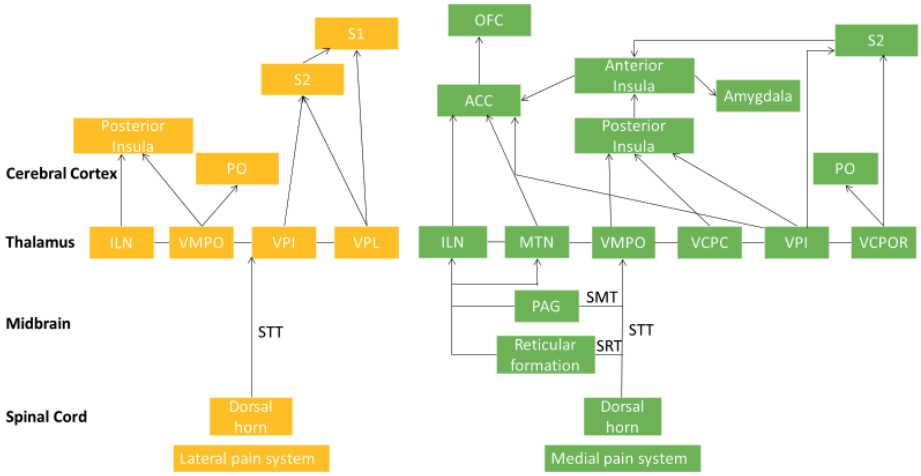

Figure 2.2. Schematic overview of (sub)cortical areas activated by the lateral and medial pain system

The lateral pain system is illustrated in yellow and the medial pain system in green. STT=spinothalamic tract; SRT=spinoreticular tract; SMT=spinomesencephalic tract; ILN=intralaminar nuclei; MTN; medial thalamic nuclei; VMPO= ventral medial posterior thalamic nuclei; VCPC; ventral caudal parvocellular nucleus; VPI; ventro posterior inferior nucleus; VCPOR= ventral caudal portae thalamic nuclei; VPL= ventral posterolateral nucleus; PO= parietal operculum; ACC= anterior cingulate cortex; OFC= orbitofrontal cortex; S2= secondary somatosensory cortex; S1= primary somatosensory cortex. This figure is based on the following literature: Apkarian et al. (2005); Bourne et al. (2014); Craig et al. (1994); Fenton et al. (2015); Garcia-Larrea and Peyron (2013); Lenz et al. (2004); Lu et al. (2016); Peirs and Seal (2016); Peyron et al. (2000); Scherder et al. (2003); Schweinhardt and Bushnell (2010); Sewards and Sewards (2002); Vogt and Sikes (2000); Woller et al. (2017)

2.3. Interaction between CT-optimal touch and acute pain

Pain and touch are closely related sensory modalities. Behaviourally, this is evident by the way we react to a painful stimulus. For instance, when we stub our toe, we tend to rub or stroke the part that hurts, to reduce the painful sensation. This reaction can be explained by the gate control theory, which is based on the notion that at the spinal level there is a 'gate' which can be 'closed' by activation of large diameter fibres (Aβ-fibres), for example rubbing, and thereby preventing the pain stimulus of reaching the cortex (Melzack & Wall, 1965). However, this theory is criticized, as its representation of the neural architecture of the spinal cord and the modulatory system exhibits oversimplifications and flaws (Moayedi & Davis, 2013). For example, the modulatory system of the Gate Control Theory does not include descending small fibres from the brainstem, which, as we now know, do play an important role in pain modulation (Moayedi & Davis, 2013).

Interestingly, there are also other types of touch associated with pain relief, namely: massage, handholding and affective touch (i.e. CT-optimal touch: Reddan et al., 2020). Their common factors are the affective and pleasant sensation that they elicit and the strong social component, hence they have also been described as interpersonal- or social touch (Goldstein et al., 2018). Recent research shows that interpersonal touch influences our well-being and can reduce stress and acute pain (López-Solà et al., 2019). Furthermore, interpersonal touch provides a feeling of social support which is also associated with a reduction of pain intensity in chronic pain and cancer patients (Goldstein et al., 2018).

Massage is possibly the most common form of interpersonal touch and often used to reduce soreness of muscles and back pain. Studies into pain modulation through massage therapy mostly focused on reducing back pain in adults (Tiffany Field, 2019). Multiple mechanisms underlying pain modulation through massage have been described, the most common of which is the aforementioned Gate Control Theory wherein deep pressure massage activates the fast conducting Aβ-fibres (Field et al., 2007). In addition, deep pressure massage is associated with an increase in vagal activity which reduces levels of cortisol which, in turn, leads to a reduction in pain (Field, 2014).

Another form of interpersonal touch is handholding. Current literature does not describe the underlying peripheral mechanism of handholding, but since it mostly involves touch on the glaborous skin, Aβ-fibres are probably involved. Recent research into handholding shows that handholding a partner can indeed reduce pain (Goldstein et al., 2018; Goldstein et al., 2017; López-Solà et al., 2019; Reddan et al., 2020). In addition, the study of Goldstein et al. (2017)

shows that during handholding, pain receiver and hand holder both show respiration and heart rate coupling, that is interpersonal physiological coupling, resulting in shared empathy for pain and emotional support. Furthermore, fMRI and EEG data showed that brain-to-brain coupling also occurs during handholding (Goldstein et al., 2018). Brain areas associated with reward, affection and emotional state are activated in both giver and receiver (Goldstein et al., 2018). The feeling of social and emotional support through handholding is associated with activation of the reward circuitry which has been linked to pain reduction. For instance, brain regions involved in the rewarding circuitry, for example OFC and dorsolateral prefrontal cortex (PFC), have been shown to project to descending pain modulatory systems (Younger et al., 2010). Thus, the analgesic effect of handholding may be explained by social understanding and support, which is rewarding and results in pain reduction (Goldstein et al., 2018; López-Solà et al., 2019; Reddan et al., 2020).

The third and more recently discovered form of interpersonal touch is CT-optimal touch, that is a gentle stroking of the skin at 3 cm/s (McGlone et al., 2014). Recent behavioural research shows that affective touch modulates acute pain experience. Habig et al. (2017) focused on the effect of CT-optimal touch on pain in healthy individuals compared to small fibre neuropathy (SFN) patients. SFN targets the thinly myelinated nerve fibres (C-fibres) and it is therefore hypothesized that the CT-fibres are impaired in this group. All participants underwent three conditions: heat pain only, CT-optimal touch only and heat pain combined with CT-optimal touch. Results show that CT-optimal touch reduces pain in healthy individuals, while the SFN patients do not experience a reduction in pain. Since the CT-fibres are not intact in these patients, this further confirms that CT-optimal touch can modulate pain through activation of the CT-fibres. However, an important limitation of the study by Habig et al. (2017) is the lack of a control touch condition.

Another study into the effect of CT-optimal touch on acute pain did use touch as a control condition and therefore provides more support for the CT-fibres' pain modulating role. Liljencrantz et al. (2017) also used a heat pain stimulus to induce pain in healthy participants, while they simultaneously received CT-optimal touch, CT non-optimal touch (i.e., fast stroking of the skin) or vibration on the skin. Results show that CT-optimal touch significantly reduces acute pain experience compared to fast non-optimal CT-stroking or vibration on the skin (Liljencrantz et al., 2017). The results of this study are consistent with a role of the CT-fibre system in pain modulation and suggest a less important role for the Aβ-fibres in pain modulation through touch. In an additional experiment conducted by Liljencrantz et al. (2017), participants received a heat pain stimulus and CT-optimal touch, but

temporal spacing between the two types of stimulation varied. The results show that pain relief was most pronounced when CT-optimal touch was applied directly before the heat pain stimulus compared to longer intervals. Furthermore, peak pain ratings are significantly lower during long stroking duration compared to short stroking duration. This suggests that the analgesic effect of CT-optimal touch does not depend on any possible distraction from the pain stimulus, when touch is applied (Liljencrantz et al., 2017).

In addition to these studies in adults, Gursul et al. (2018) investigated the effects of CT-optimal touch on pain experience in infants, who received a clinical heel lance for blood collection. Ten seconds prior to the heel lance one group received CT-optimal touch and one group received no touch. To measure behavioural responses, the pain related facial expression was recorded. Results show that both groups exhibited facial grimacing, but the duration was 50% shorter for infants receiving CT-optimal touch. Compared to research in which pain was experimentally induced, this research shows that CT-optimal touch can also reduce experienced pain during a medical procedure. In sum, these behavioural studies indicate that CT-optimal touch can reduce acute pain experience in adults and infants.

In an effort to understand the neurophysiology behind these behavioural effects of CT-optimal touch on pain, several studies suggest that the CT-afferent system can modulate pain through a bottom-up process starting in the dorsal horn of the spinal cord (Gursul et al., 2018; Habig et al., 2017; Krahé et al., 2016; Lu & Perl, 2003; von Mohr, Krahé, et al., 2018). Furthermore, the CT-afferent system activates several brain areas, for example the insula and ACC, that are not only associated with the affective and subjective evaluation of touch, but also with the subjective appreciation of pain that is the medial pain system (illustrated in Figures 2.1 and 2.2). Therefore, it could be that pain modulation by the CT-system also occurs at supraspinal levels. This implies that there are possibly two ways through which the CT-afferents can modulate pain processing, referred to as the inhibitory system and the downregulating system. This is illustrated in Figure 2.3.

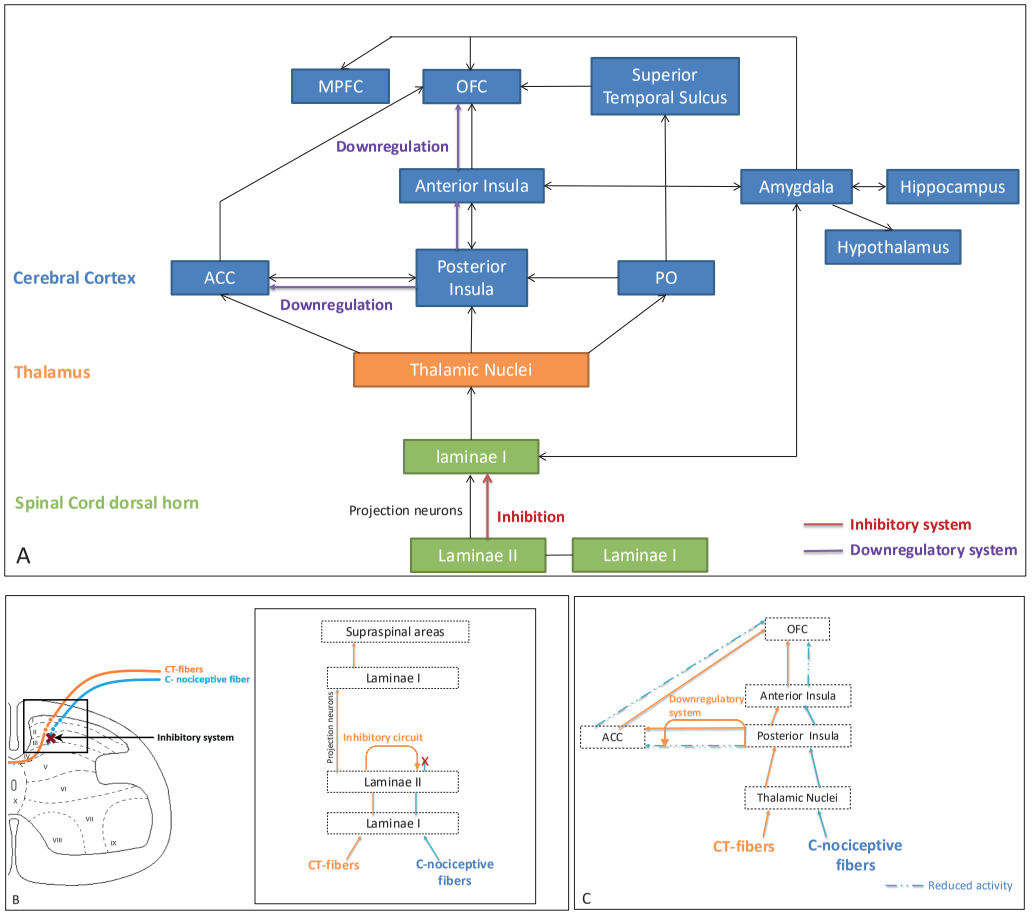

Figure 2.3. (a) schematic overview of the CT-afferent system including the two ways of pain modulation. The red line represents the inhibitory system within the dorsal horn. The purple line represents the downregulating system within cortical brain areas. **(b)** Dorsal horn inhibitory system. **(c)** Cortical downregulatory system. ACC= anterior cingulate cortex; PO= parietal operculum; OFC= orbitofrontal cortex; MPFC= medial prefrontal cortex. Figure is based on the following literature: Gursul et al. (2018); Habig et al. (2017); Liljencrantz et al. (2017); Lu and Perl (2003); Marshall and McGlone (2020); Shaikh et al. (2015); von Mohr, Krahé, et al. (2018).

First, electrophysiological research in animals shows that neurons within laminae II of the spinal dorsal horn contain a specific inhibitory pathway related to CT-afferent input (Lu & Perl, 2003). The laminae II neurons activated by CT-afferent projections inhibit laminae II neurons receiving nociceptive input. This prevents nociceptive input from reaching laminae I and thereby (sub)cortical brain regions involved in pain processing. This inhibitory circuit could represent the way innocuous impulses suppress nociceptive impulses (Habig et al., 2017; Liljencrantz et al., 2017; Lu & Perl, 2003).

Second, several human studies show that the CT-afferent system also modulates the activation of brain areas related to pain processing. In addition to the behavioural experiment of Gursul et al. (2018), they investigated the effect of CT-optimal touch versus CT non-optimal touch on noxious-evoked brain activity measured with EEG in infants who received a pinprick. Results show that CT-optimal touch significantly reduces the magnitude of noxious evoked brain activity compared to CT non-optimal touch. Furthermore, Krahé et al. (2016) studied the effect of CT-optimal touch versus CT non-optimal touch on laser-evoked potentials (LEP's) to noxious stimulation. The results show that CT-optimal touch reduces the LEP's local peak amplitude on the N1 complex. The N1 reflects early stages of pain processing mostly occurring outside conscious awareness. They find no effect of CT-optimal touch on the N2-P2 complex, which is thought to reflect higher order processing of pain, mostly associated with the socio-cognitive aspects of pain experience (Krahé et al., 2016; Krahé et al., 2015). Based on the study of Krahé et al. (2016), von Mohr, Krahé, et al. (2018) investigated the effect of CT-optimal touch versus CT non-optimal touch applied *by a romantic partner* on laser-evoked potentials (LEP's) to noxious stimulation. CT-optimal touch significantly reduces the LEP's local peak amplitude on the N1 as well as the N2-P2 complex. As mentioned, the N2-P2 complex is associated with higher order conscious processing of pain, mostly linked to activity in the anterior insula and the ACC, considered important for the motivational and affective aspects of pain (von Mohr, Krahé, et al., 2018). The reduced LEP's peak in the N2-P2 complex suggests that when CT-optimal touch is applied by a romantic partner together with a noxious stimulus, the pain related processing in the anterior insula and ACC show downregulation, which may modulate the motivational aspects of pain (Habig et al., 2017; Shaikh et al., 2015; von Mohr, Krahé, et al., 2018).

However, fMRI data from the study of Habig et al. (2017) appears inconsistent with the findings of von Mohr, Krahé, et al. (2018) and Krahé et al. (2016). Here, no significant differences in cortical activation were found between noxious stimulation with and without CT-optimal touch, even though participants did

report a reduction in pain when CT-optimal touch was applied (Habig et al., 2017). Therefore, it may be argued that the downregulation of the N1 and N2-P2 complexes, as demonstrated by von Mohr, Krahé, et al. (2018) reflects pain modulation through the aforementioned bottom up processes in the spinal dorsal horn. However, in the same study of von Mohr, Krahé, et al. (2018) pain modulation through CT-optimal touch could not be based on the inhibitory circuitry within the spinal dorsal horn. In this study, the tactile stimulus and pain stimulus were delivered at different times and different body parts, which were therefore unlikely to interact at spinal levels, providing evidence for a pain modulating role of the CT-system through higher order mechanisms in the insula and ACC. In addition, this study also showed that the effectiveness of pain modulation through CT-fibre stimulation depends on social factors and perceived feelings of social support. This is in line with previous research suggesting that the perceived pleasantness of CT-optimal touch is linked to the affective and interpersonal properties of this kind of touch (McGlone et al., 2014). Moreover, research into pleasure related analgesia reveals that pleasurable sensations provide top-down modulation of nociception (Leknes & Tracey, 2008), which may be linked to PFC and insula activation, regions also strongly involved in CT-optimal touch (Leknes & Tracey, 2008; I. Morrison, 2016). Given the strong connection between CT-fibre activation and perceived pleasantness of the touch (Björnsdotter et al., 2010), it could be that the CT-system also reduces pain through top-down pleasure-related analgesia.

Taken together, these studies provide substantial behavioural and neural evidence supporting a pain modulating role for CT-optimal touch. Based on these studies, a novel model illustrating the neurophysiology of the CT-afferent system, and its pain amelioration can be introduced (see Figure 2.3). Figure 2.3b shows the proposed inhibitory system within the dorsal horn of the spinal cord. This system inhibits the pain stimulus from reaching ascending pathways and thereby prevents further cortical processing, resulting in pain reduction. Furthermore, Figure 2.3c illustrates pain modulation through downregulation of the insula and ACC, both important for the processing of the subjective experience of pain. Currently, it is unclear whether this downregulation is a result of the bottom-up inhibitory system that is the inhibitory system prevents the pain stimulus from reaching the brain resulting in reduced activation at cortical levels measured with EEG – or the result of modulation through the insula and ACC itself. Further research into the exact neural mechanism should clarify the contradictory evidence for modulation at a cortical level.

As described previously, CT-optimal touch is not the only type of interpersonal touch associated with pain reduction. However, compared to CT-optimal touch, the pain modulating role of massage therapy seems to be

based on different processes. Unfortunately, there are no studies into the neurophysiology of massage, and the studies that have been conducted suffer from several methodological limitations which makes it difficult to understand the underlying mechanism of massage (Tiffany Field, 2019).

In contrast, handholding and CT-optimal touch appear to rely on similar cortical processes for pain modulation. Both types of touch are interpersonal-social types of touch and depend on the activation of brain areas associated with affection and reward, which are important for their pain modulating role (Krahé et al., 2016; López-Solà et al., 2019). Hypothetically, it is possible that these two types of interpersonal touch rely partially on the same social and affective brain network. CT-optimal touch relies on direct CT-fibre input, thereby activating this affective network. Handholding may rely on indirect activation of this affective network through the social and affective aspects of this kind of touch. Interestingly, recently published research shows that CT-afferents not only innervate the human hairy skin but also the glaborous skin of the hand (Watkins et al., 2021). Although the density is much lower than in hairy skin, it could explain why slowly touching the palm of the hand is also perceived as pleasant and why handholding reduces pain (Watkins et al., 2021).

2.4. Clinical implications

The described modulating role of the CT-system on acute pain experience raises the question: might CT-optimal touch also reduce chronic pain?

The underlying mechanisms of chronic pain are still not completely understood, but studies do show that in musculoskeletal pain, osteoarthritis and neuropathic pain there are changes in the structural and functional connectivity of brain regions involved in pain processing. Especially the insula, ACC and PFC appear to show changes in connectivity which are linked to an increase in pain intensity and clinical pain duration (Kuner & Flor, 2016; Schmidt-Wilcke, 2015). Because of the mostly unknown underlying mechanisms of chronic pain, it is hard to find a suitable treatment. Currently, treating chronic pain is based on a multimodal approach in which pharmacological, non-pharmacological and physical rehabilitation are combined. Unfortunately, there are still many people suffering from chronic pain (Bicket & Mao, 2015).

Based on the presented research, CT-optimal touch could be a promising candidate in reducing chronic pain. Indeed, a recently published paper of Di Lernia et al. (2020) shows that CT-optimal touch significantly reduces the severity of reported pain in chronic pain patients by 23% after

11 min of stimulation. Participants suffered from primary chronic pain, secondary musculoskeletal pain and neuropathic pain and received either CT-optimal touch or vibration on the skin. The effect of CT-optimal touch was independent of pathological condition (Di Lernia et al., 2020). Even in central and peripheral neuropathic pain its severity appears reduced by CT-optimal touch. This is unexpected since research also links CT-fibre stimulation to tactile allodynia, a symptom of neuropathic pain in which innocuous stimuli elicit a painful burning sensation. Since CT-optimal touch is gentle stroking of the skin this could elicit tactile allodynia (Nagi et al., 2011). However, even before CT-fibres were discovered, it was suggested that Aβ-fibres elicit allodynia following central sensitization in the dorsal horn, a notion that is also suggested by recent research (Liljencrantz & Olausson, 2014). This could explain why CT-optimal touch and skin vibration did not elicit a painful sensation in the study of Di Lernia et al. (2020) and, more importantly, why CT-optimal touch reduced the experienced chronic pain. As described in the previous section and illustrated in Figure 2.3, pain modulation through the CT-system may depend on multiple neural mechanisms that may downregulate the possible overactivation of the ACC and PFC in chronic pain resulting in a decrease in experienced pain severity (Gursul et al., 2018; Krahé et al., 2016; Lu & Perl, 2003; Schmidt-Wilcke, 2015; von Mohr, Crowley, et al., 2018). Overall, CT-optimal touch seems very promising for reducing chronic pain.

Therefore, it would be of interest to study whether CT-optimal touch can reduce chronic pain in other clinical patient groups. In neurodegenerative diseases, chronic pain is very common. In mild to moderate stages of Alzheimer's Disease (AD), 38 – 75% are suffering from chronic pain. It seems that the descending pain pathways are affected leading to an increase in pain (de Tommaso et al., 2016). Given the course of AD, it is expected that the CT-fibres are intact as these systems are unaffected, however this has not been studied yet. So, in AD CT-optimal touch could alleviate pain, but only in mild to moderate stages as in later stages ascending pathways seem affected leading to a reduction in pain (de Tommaso et al., 2016). Another patient group suffering considerably from chronic pain is Multiple Sclerosis (MS), with a prevalence of 50 – 86% (de Tommaso et al., 2016). The underlying mechanisms causing pain in MS are not yet understood, but it seems plausible that there are alterations in the pain network caused by demyelization (Borsook, 2012). We argue that the CT-fibres are still intact in MS, as they are not myelinated. If CT-optimal touch could modulate pain in MS it is more likely to occur at the dorsal horn of the spinal cord, because demyelization could also affect cortical areas related to CT-optimal touch. Finally, in Parkinson's Disease (PD)

30 – 95% are suffering from chronic pain (Blanchet & Brefel-Courbon, 2018). This is caused by overactivation of regions involved in pain processing, especially the ACC and insula (Antonini et al., 2018; Tseng & Lin, 2017). Interestingly, a recent study revealed that PD patients, similar to healthy participants, report higher pleasantness ratings for CT-optimal stroking velocities compared to higher or lower stroking velocities (Kass-Iliyya et al., 2017). This suggests that CT-optimal touch is perceived and processed in the same way in PD patients as in healthy controls. This finding makes CT-optimal touch a promising candidate to reduce pain in PD.

Overall, based on the aforementioned studies, CT-optimal touch may reduce pain in these patient groups and may therefore be useful as a new, alternative or supplementary pain intervention (Di Lernia et al., 2020; Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018). If proven effective, it may be implemented in daily care routines in which a partner or caregiver provides CT-optimal touch, as this appears to increase its beneficial effects (von Mohr, Krahé, et al., 2018). Based on the duration of perceived pleasantness of CT-optimal touch, a duration of approximately 10 – 15 min is proposed (Sailer et al., 2016). This kind of intervention can take place from home and it does not involve trained therapist, which makes it easy to apply and implement in daily life. Based on the aforementioned studies CT-optimal touch may not diminish pain completely, it is therefore more likely that it can be used complementary to existing pain treatments.

2.5. Conclusion

In summary, pain and CT-optimal touch (affective touch) depend on partially overlapping neural mechanisms. Recent research has focused on the neural process underlying CT-optimal touch and how they possibly influence the processing of pain and pain experience. Several studies show that CT-optimal touch can reduce acute pain experience, and a few studies have investigated the underlying neurophysiological mechanism for this modulating role of CT-optimal touch. With the current review we aimed to provide an overview of recent research and knowledge about affective touch and pain, and how they can interact. The latter is illustrated by a novel model (Figure 2.3).

This modulating function of CT-optimal touch makes it a promising candidate for new interventions. Importantly, recent experimental research shows that CT-optimal touch can reduce chronic pain in a variety of patient groups. Based on these findings, it would be interesting to study whether CT-optimal touch could also be implemented as a treatment for chronic pain

as there are several clinical populations, for whom current pain treatments are not sufficient.

2.6. Search strategy and selection criteria

A literature search was conducted to find relevant articles on pain and affective/CT-optimal touch (Figure 2.4). The following databases were used: PubMed, Embase and Cochrane. For the pain literature as selection criteria, the following search terms were used: pain physiology, pain perception, nociceptor physiology, nociception and chronic pain. Including filters: publication last 10 years, review, human species. This provided 605 articles. Subsequently, the title and abstract were screened based on the following selection criteria: acute pain, chronic pain, physiology, pathophysiology and anatomy. In addition, literature focusing on specific diseases and/or pain syndromes (e.g., migraine, musculoskeletal pain) were excluded. This led to exclusion of 421 articles. There were 38 articles excluded as these were duplicates. This led to N= 605 – 459 = 146 possible relevant articles. The full text of these 146 articles was analysed to determine relevancy, resulting in 50 articles selected. Because of content overlap within certain articles and cross references, 29 were eventually used.

For the affective/CT-optimal touch literature, the following search terms were used: affective touch, gentle touch, CT-afferents. No filters were added. This provided 135 articles. For title and abstract screening the following inclusion criteria were applied: physiology, brain, cortical, processing; as well as the following exclusion criteria: social touch, infants. This resulted in 34 articles (i.e., 101 articles were excluded). Ten articles were duplicates and excluded as well. Based on abstract and/or full text analyses, all 24 remaining articles were relevant and used for this review. A literature search on 'affective touch and pain' and 'CT fibres and pain' resulted in eight additional relevant articles.

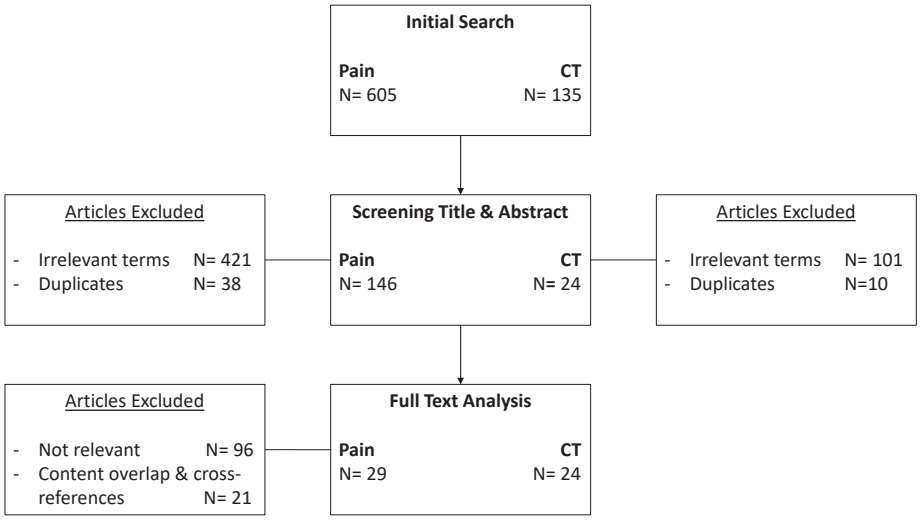

Figure 2.4. Flowchart illustrating the screening and selection process for paper inclusion

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Conflicts of interest

All authors declare no conflict of interest.

Author contribution

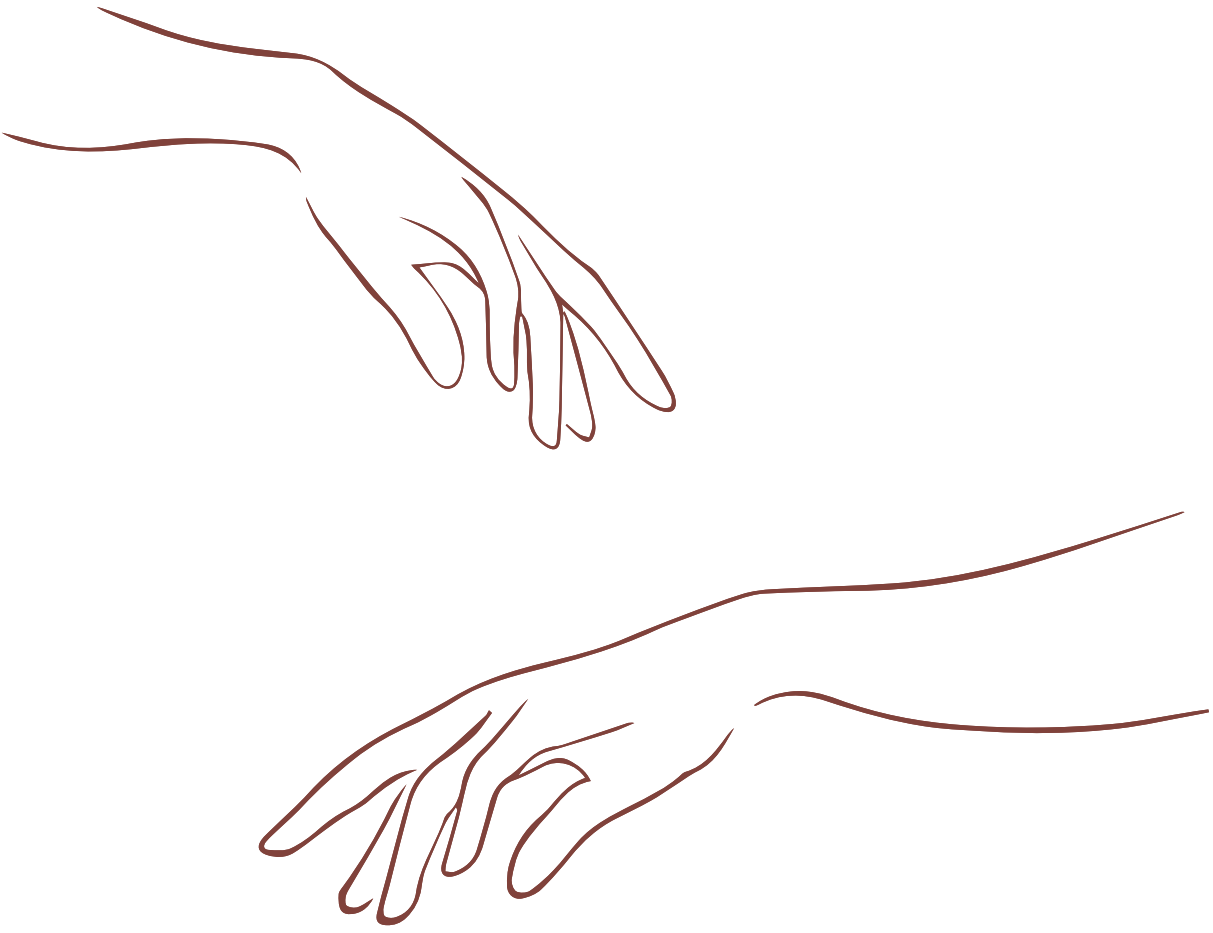
Larissa Lauren Meijer (Conceptualization; Funding acquisition; Writing – original draft; Writing – review & editing) C. Ruis (Conceptualization; Supervision; Writing – original draft; Writing – review & editing) M. J. van der Smagt (Conceptualization; Funding acquisition; Supervision; Writing – original draft; Writing – review & editing) E. J. A. Scherder (Conceptualization; Funding acquisition; Supervision; Writing – original draft; Writing – review & editing) H. C. Dijkerman (Conceptualization; Funding acquisition; Supervision; Writing – original draft; Writing – review & editing).

Data availability statement

Data sharing not applicable to this article as no data sets were generated or analysed during the current study.

2

Chapter 3



Affective touch reduces electrically induced itch experience

Larissa L. Meijer
Zoë A. Schielen
Kim Y. van Ree
H. Chris Dijkerman

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Abstract

Introduction

Itch is a common symptom in dermatologic and other diseases and can have a severe impact on quality of life and mental health. As a proportion of patients with itch-symptoms is resistant to commonly used anti-histamine treatments, development of new treatments is desirable. Past research on pain, itch and affective touch (i.e. slow, gentle stroking of the skin activating C-tactile fibers) revealed an inhibitory relationship between affective touch and pain and between pain and itch. Given the overlap in neural processing between these three sensory submodalities, a possible interaction between affective touch and itch might be expected. This study investigated whether there is a relationship between itch and affective touch, and if so, whether affective touch inhibits itch.

Methodology

Itch was electrically induced with the use of electrodes that were placed at the ventral side of the wrist of 61 participants. A within-subject design was conducted with two conditions. An experimental -affective touch- condition (stroking the forearm with a soft brush at 3 cm/s) and a control -non-affective touch- condition (stroking the forearm with a soft brush at 18 cm/s). Touch was applied on the dorsal side of the forearm, the same arm as where the electrodes were placed. For each condition itch was induced for 20 min, with every 2 min a VAS-scale measurement of the level of experienced itch.

Results

Both types of touch reduced the experienced itch compared to baseline ($p < 0.01$, partial = 0.67). However, affective touch had an additional significant relieving effect compared to non-affective touch ($p = 0.03$, partial = 0.08). The alleviation of itch started after 2 min of stroking and continued to increase up till 6 min, where after the relieving effect stabilized but still persisted.

Conclusion

This finding suggests that affective touch, as with acute pain, has a relieving effect on electrically induced itch.

Keywords: itch, affective touch, C-fibers, somatosensory, relief

3.1. Introduction

Itch is a common symptom in dermatological diseases and is defined as "an unpleasant sensation causing the urge to scratch" (Drzezga et al., 2001). Itch is a commonly experienced problem, with a prevalence of 8.4% in the general population. In addition, the lifetime prevalence of chronic itch is even higher with 22%, meaning that one out of five people will experience chronic itch (Weisshaar, 2016). Furthermore, the burden of itch is comparable to the burden that is experienced during chronic pain and itch symptoms can significantly impact quality of life and mental health as well (Bathe et al., 2009; Desai et al., 2008; Jafferany & Davari, 2019; Kini et al., 2011; Lee et al., 2017). Studies indicated that higher scores on an itch intensity scale in patients with dermatological diseases causing itch were related to a higher score on depression scales (Lee et al., 2017; Misery et al., 2007). In addition, a study by Schneider et al. (2006) showed that 70% of the patients in a sample of 109 participants with dermatological diseases causing itch had one to six psychiatric disorders. Given the high prevalence and impact of itch, it seems a worldwide problem (Bathe et al., 2009).

One aspect of itch that has been researched considerably is the neurophysiological basis of itch. In 1997, itch-selective neurons were discovered in humans (Schmelz et al., 1997). Research indicated that these neurons were part of a broader category of neurons called C-afferents. These C-afferents are characterized by their lack of myelination and therefore have a slow conducting speed (Drzezga et al., 2001; Ikoma et al., 2006; Schmelz et al., 1997). After activation of the C-fibers, the signal is transported to the dorsal horn of the spinal cord from which signals are projected to the thalamus, somatosensory cortex, sensorimotor cortex, posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), insular cortex and the basal ganglia with the putamen (Dhand & Aminoff, 2014; Wallengren, 2005). The involvement of the ACC contributes to the affective component of itch (Wallengren, 2005).

Furthermore, subsequent research implied that the itch-selective neurons were sensitive to histamine, mostly associated with acute itch experience (Fowler & Yosipovitch, 2019; Ständer & Schmelz, 2006). However, recent research revealed that some of these neurons do not respond to histamine, but are activated by other substances and stimuli (Johanek et al., 2007). Consequently, a proportion of patients with itch symptoms is resistant to commonly used anti-histamine treatments (Ikoma et al., 2005; Johanek et al., 2007). It seems that especially chronic itch conditions are associated with non-histamine sensitive neurons and therefore respond better to treatments targeting the nerves than

the immune system (Fowler & Yosipovitch, 2019). Given the impact of (chronic) itch, development of new suitable treatments is needed.

The development of new treatments could be inspired by research on another sensory modality that affects itch, namely pain. During the processing of pain, brain areas such as the insular cortex, cingulate cortex and premotor areas are activated (Bourne et al., 2014). As mentioned, these brain areas are also highly involved in the processing of itch (Wallengren, 2005). This shows the close relationship between these senses at supraspinal level (Bourne et al., 2014; Ikoma et al., 2006; Ständer & Schmelz, 2006). In addition, itch and pain also seem to affect each other at a behavioral level: research confirmed that painful sensations can reduce itch sensations, which explains why we scratch our skin during itch (Ikoma et al., 2003; Ikoma et al., 2006; Ständer & Schmelz, 2006). Scratching activates interneurons in the dorsal horn of the spinal cord. These interneurons subsequently inhibit the transduction of C-afferent signals involved in itch (Chuquilin et al., 2016; Davidson & Giesler, 2010; Liu & Ji, 2013). Because the itch-signal is inhibited by pain, the transduction of the signal from the dorsal horn of the spinal cord toward the thalamus is reduced which results in a reduction of itch sensations.

Reducing itch by evoking pain (e.g., scratching) can only be a temporary solution as it is unpleasant and can cause serious skin inflammation when used on a permanent basis. However, the interaction between pain and other systems might provide useful information on which new interventions to reduce itch can be based. An example is the interaction between pain and affective touch. Affective touch activates another subgroup of C-afferents, known as C-tactile or CT-afferents (Gordon et al., 2013; Olausson et al., 2002; Triscoli et al., 2013). CT-afferents are located mainly in the hairy skin and respond to slow and gentle stroking of the skin, consisting of velocities between 1 and 10 centimeters per second, with an optimal response at 3 centimeters per second, which provides a pleasant sensation (Gordon et al., 2013; Löken et al., 2009; Morrison et al., 2011). The CT-afferents transmit signals through the dorsal horn of the spinal cord to the thalamus, insula, anterior cingulate cortex (ACC), prefrontal cortex and amygdala (I. Morrison, 2016). Recent research shows that affective touch and pain influence each other as well: affective touch has an inhibitory effect on acute pain (Habig et al., 2017; Liljencrantz et al., 2017). It seems that affective touch can inhibit pain at the level of the dorsal horn of the spinal cord by a specific inhibitory pathway related to CT-fiber input (Lu & Perl, 2003). In addition, Gursul et al. (2018) and von Mohr, Krahé, et al. (2018) showed that at a supraspinal level, affective touch reduces activation of areas related to pain processing, namely the insula and anterior cingulate cortex. In sum, affective touch and pain share neural characteristics that are comparable to the similarities between pain and itch.

Furthermore, affective touch seems to inhibit pain, as is the case for the effect of pain on itch.

The evident similarities between brain areas involved in itch, pain and affective touch, and the inhibitory behavioral effects of pain on itch and affective touch on pain, suggest that affective touch might have a relieving effect on itch (Chuquilin et al., 2016) and the current study will research this. Itch will be induced by an electrical current stimulator, as recent research shows that this is a reliable way of inducing itch (Ikoma et al., 2005; van Laarhoven et al., 2017). The relieving effect of affective touch on itch will be evaluated by testing the decrease in perceived itch in two conditions. Affective touch will be used in the experimental condition, and non-affective touch (stroking with a velocity of 18 cm/s) will be used in the control condition. Itch induction and touch stimulation will be provided simultaneously for 20 min. This time-frame is based on recent research of Sailer et al. (2016) showing that the activation of brain areas related to affective touch and the perceived pleasantness of affective touch stabilizes after 20 min. Therefore, we expect that, if there is a relieving effect of affective touch, it will persist for approximately 20 min.

In addition, perceived pleasantness of affective touch will be monitored, and the relationship between pleasantness of affective touch and its relieving effect on itch will be researched. It is expected that experiencing affective touch as more pleasant is associated with experiencing more itch relief from affective touch (Pawling et al., 2017; Perini et al., 2015). A factor that modulates how intensely itch is experienced is the amount of attentional focus. Research suggests that a high attentional focus to bodily sensations such as itch, increases the amount of experienced itch (van Laarhoven et al., 2010). Therefore, we will additionally investigate whether there is a relation between high awareness to bodily sensations and the alleviation of itch by affective touch. We expect that people who have a high attentional focus to bodily sensations, experience less relief from affective touch (Verhoeven et al., 2006).

3.2. Methods and materials

3.2.1 Participants

An a priori calculation for the repeated measures ANOVA (f = 0.2, α err prob. = 0.05, power = 0.95, number of groups = 2, number of measurements = 11) recommend a sample size of 30. Eventually, 69 participants signed up for participation out of which 61 participants were eligible for participation. The study group consisted of 12 men (Mage = 27.50, range age = 18 – 28) and 49 women (Mage = 21.61, range age = 18 – 53). Of the participants, 54.1% were following or had finished tertiary education, 45.9% had finished secondary education. The participants were recruited through the Social and Behavioral Sciences research participation system (SONA) of Utrecht University. Participants from the age of 18 and older, and fluent in the Dutch language were eligible to participate in this experiment. People suffering from a skin condition where itch is a present symptom, like chronic itch or psoriasis, or people using a pacemaker, were excluded from this experiment. People using a pacemaker were not allowed to participate because of the electrical stimulation that could interfere with the functioning of the pacemaker. The faculty ethical review board of the University of Utrecht approved the study's protocol and all participants gave permission for participating in this experiment by means of a written informed consent.

3.2.2 Materials

3.2.2.1 Demographical Information

To verify the inclusion and exclusion criteria the participants were asked to state their age, gender, highest completed education, whether they were suffering from skin conditions, and whether they were using a pacemaker.

3.2.2.2 Pain and Vigilance Attention Questionnaire (PVAQ)

To examine the awareness to bodily sensations, an adjusted version of the Pain Vigilance and Awareness Questionnaire (PVAQ) was used (McCracken, 1997). Originally, this questionnaire was focused on pain. As claimed by van Laarhoven et al. (2017), the questionnaire is suitable to investigate itch, when changing the word "pain" to "physical sensations". This alteration had no consequences for the reliability or validity of the PVAQ. The questions of the PVAQ focus on sensing, ignoring and monitoring bodily sensations. The PVAQ consists of 16 items, which are scored on a 6-point Likert scale. Zero represents "never", 5 represents "always". Items 8 and 16 should be reverse-scored before the total score of the PVAQ can be calculated. A relatively low score on the PVAQ

indicated low attention to bodily sensations. A relatively high score represented high attentional focus on bodily sensations.

3.2.3 Itch Induction

An electrical stimulus was used to induce itch. According to Ikoma et al. (2005) and van Laarhoven et al. (2017), using a constant current stimulator (Isolated Bipolar Constant Current Stimulator DS7, Digitimer, United Kingdom) is a reliable way to induce itch. Nerve stimulation electrodes were attached to the ventral side of the wrist, alternately to the right or left wrist equally divided among the participants. The DS7 had a default setting where the pulse duration was set at 100 milliseconds and the compliance voltage was set at 200 volts. E-prime 2.0 (Psychology Software Tools, 2015) was used to alter the pulse duration of the DS7. A transmission of a constant stimulation of 50 Hz by having a pulse duration of 20 milliseconds was programmed. These pulses were active for 0.2 milliseconds and inactive for 19.8 milliseconds. The level of amperage (in milliampere) was individually adjusted prior to the experiment and was determined based on the participants' experienced level of itch. A stimulation period of 4 s was used to test the itch stimulation, the experienced itch was rated on the VAS. After each VAS rating, the amperage was increased, by steps of 0.1 – 0.2 mA, until the participants considered the experienced itch a 7 or higher on the VAS. If participants did experience itch but did not report higher than a 7 on the VAS, the highest rating of the experienced itch was registered. The corresponding amperage was used in the experiment. The level of amperage ranged from 1.80 to 4.90 ($M_{amperage}$ = 3.02, $SD_{amperage}$ = 0.76). When participants did not experience any itch or the experienced itch intensity was not rated with a three or higher, the experiment was discontinued.

3.2.4 Affective and Non-Affective Touch

The (non-)affective touch stimulation was executed by stroking with a soft foundation brush. The velocity of stroking in the experimental affective touch condition was 3 centimeters per second. The velocity of stroking in the control non-affective touch condition was 18 centimeters per second. The researcher marked the length of 6 centimeters on the dorsal side of the arm to which the electrode was attached. This enabled the researcher to stroke with the correct velocity during the affective touch and non-affective touch condition (thus in the affective touch condition, the 6 cm length was stroked over 2 s, while in the non-affective touch condition the 6 cm length was stroked 3 times per second).

3.2.5 Monitoring Sensations

3.2.5.1 Visual Analog Scale (VAS) for itch

To measure itch, participants were asked to indicate the degree of itch they experienced on a scale of 0 to 10. Zero represented "no itch" and 10 represented "unbearable itch".

3.2.5.2 VAS for Pleasantness

To measure the experienced pleasantness of stroking, participants were asked to rate the experienced pleasantness on a scale that ranged from 0 to 10, where 0 represented very unpleasant" and 10 represented "very pleasant".

The VAS is evaluated as a reliable and valid assessment to measure itch and pleasantness (Phan et al., 2012; Sailer et al., 2016).

3.2.6 Procedure

Prior to the experiment participants filled in the demographical details and the PVAQ. The baseline itch intensity was registered before each condition. Hereafter, the baseline pleasantness of touch was determined and registered by stroking the arm for 10 s over the 6 cm outline at either affective or non-affective touch velocities. The participant underwent an experimental and control condition which both had a duration of 20 min, the order was randomized between subjects. Between the conditions there was a 10 min break. Each condition had 10 blocks of 2 min simultaneous stimulation from the DS7 and stroking. Immediately following every 2 min of itch stimulation and stroking, the participants were asked to rate the experienced itch on the VAS. This took ~ 10 sec. Hereafter the next 2 min of itch stimulation and stroking started (Figure 3.1).

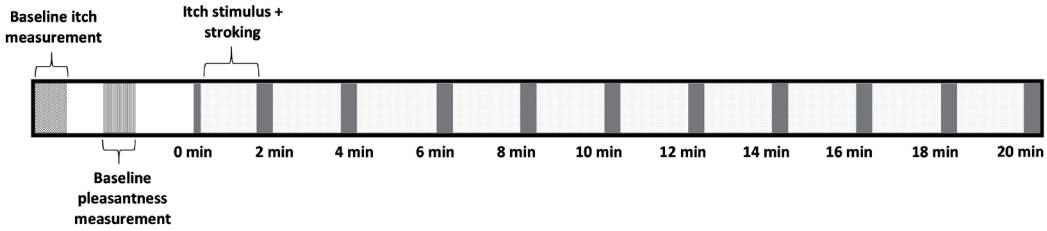

Figure 3.1. Outline in time of a single condition

3.2.7 Statistical Analysis

Data was analyzed using SPSS Statistics (version 26). Eight participants were excluded and the experiment was discontinued because they did not experience itch.

Data was checked for normal distribution. For the VAS itch intensity scores, which were analyzed with a repeated measures ANOVA, the residuals were used. According to the Shapiro – Wilk test most variables were not normally distributed, but the Shapiro – Wilk test is shown to be too sensitive in a large sample size (>50). Therefore, data was also visually inspected using the Q – Q plots and histograms, these showed that the data was approximately normally distributed. Based on these factors, together with the large sample size (>60), we decided that parametric testing was permitted (Field, 2013; Ghasemi & Zahediasl, 2012). The sphericity was mildly violated, therefore the Greenhouse-Geisser Epsilon output was used.

The VAS pleasantness scores were also checked for normality. The VAS scores for pleasantness in the affective touch condition violated the assumption of normality. The VAS scores for pleasantness in the non-affective condition did not violate the assumption of normality. The differences between the pleasantness of touch in the affective and non-affective condition were checked with a paired *t*-test.

In order to analyze the difference between the effect of affective touch and non-affective touch on itch, a repeated measures ANOVA was conducted, with touch (affective and non-affective touch) and time (baseline and the 10 timepoints within a 20 min period on which itch was measured) as independent variables and the experienced itch measured with VAS scores as dependent variable.

To analyze the changes in the relieving effect of affective touch on itch over time, a repeated measures ANOVA with contrasts (follow-up analysis) was conducted with the itch ratings from the experimental and control conditions excluding the baseline itch measurements. Every 2 min itch measurement was compared to the first 2 min itch measurement. This resulted in nine contrast analyses.

To assess the effect that attention to bodily sensations has on the effect of affective touch on itch, a Spearman correlation with the difference scores between itch ratings in the non-affective and affective touch conditions and the PVAQ scores was conducted. The mean of the 10 measurements in the non-affective condition was subtracted from that of the affective condition. Two assumptions for the Pearson correlation were violated, therefore a non-parametric Spearman correlation was conducted.

To analyze the influence of individual differences in experienced pleasantness on the relieving effect of affective touch, the difference scores of pleasantness were correlated with the difference scores of itch. The difference scores of pleasantness were calculated by subtracting the VAS pleasantness

score in the non-affective condition from those in the affective condition. The difference score of itch was calculated by subtracting the mean itch VAS scores in the non-affective touch conditions from those in the affective touch condition. The assumptions of normality and linearity were violated, a Spearman correlation was conducted. All results displayed are means ± SE, unless otherwise stated. A $p < 0.05$ is considered statistically significant.

3.3. Results

The baseline data and experimental data of itch and pleasantness and the PVAQ scores are displayed in Table 3.1. The baseline itch measured in the affective and non-affective condition were comparable (6.80 ± 0.16 and 6.75 ± 0.21, respectively, $t(60) = 0.23$, $p = 0.82$).

A two tailed, paired samples *t*-test was used to compare the VAS scores of pleasantness for the affective touch and non-affective touch condition (Table 3.1). The VAS scores for pleasantness in the affective touch condition were statistically significantly higher than the VAS scores for pleasantness in the non-affective touch condition, $t(60) = 5.07$, $p < 0.01$. Cohen's *d* for this test was 0.89, which can be described as large.

3.3.1 Relieving Effect of Touch Relative to Baseline Itch Measurements

A 2 (touch: affective touch vs. non-affective touch) × 11 (time point: the VAS scores of the baseline itch measurement and the 10 itch measurements of after each 2 min itch stimulation) repeated measures ANOVA was used to investigate the relieving effect of touch on itch.

A significant main effect for touch was obtained, $F(1,60) = 4.87$, $p = 0.03$, partial = 0.08 (Figure 3.2). The VAS scores for itch were significantly lower during the affective touch condition than during the non-affective touch condition (Table 3.1, Figure 3.2). A significant main effect was also reported for time point, $F(2.58, 154.61) = 28.72$, $p < 0.01$, partial = 0.32 (Figure 3.2). A contrast analysis was conducted to compare the baseline VAS scores with the other timepoints. There were significant differences between the baseline itch VAS score and the experimental itch VAS scores in both the affective and non-affective touch conditions $F(1,60) = 121.24$, $p < 0.01$, partial = 0.67). The interaction between touch and time point was not significant, $F(4.92, 295.14) = 1.75$, $p = 0.12$, partial = 0.03 (Figure 3.2).

3.3.2 Relieving Effect of Touch for Experimental Itch Ratings

A 2 (touch: affective touch vs. non-affective touch) × 10 (time point: the VAS scores the 10 itch measurements after each 2 min itch stimulation) repeated measures ANOVA was conducted to measure the effect of touch over time. The VAS scores for itch in the affective touch condition were significantly lower than the VAS scores for itch in the non-affective touch condition, which illustrates a main effect for touch, $F(1,60) = 5.01$, $p = 0.03$, partial = 0.07. The VAS scores for itch within each condition differed significantly over time, which illustrates a main effect for time point, $F(2.08, 124,79) = 3.33$, $p = 0.04$.

There was no significant interaction effect found for touch × time point, $F(4.10, 245.71) = 1.30$, $p = 0.27$, in the ANOVA analysis. Although the interaction was not significant, as we did expect changes over time with respect to the difference in itch between conditions and after visual inspection of the data (Figure 3.3), it seemed of interest to conduct a follow up contrast analyses for the interaction. The 2 min vs. 4 min itch measurements differed significantly, thus the difference in itch ratings between affective and non-affective touch were significantly larger at 4 min compared to 2 min, $F(1,60) = 4.66$, $p = 0.03$, partial = 0.07 (Table 3.2, Figure 3.3). A similar difference was found for the VAS scores for itch at 6 min compared to the 2 min measurement, $F(1,60) = 9.19$, $p = <0.01$, partial = 0.13 (Table 3.2, Figure 3.3). Further details about the contrast analyses are stated in Table 3.2.

Table 3.1. The mean scores, SE and range of VAS scores of the affective and non-affective touch condition, the PVAQ score and the difference scores of itch and pleasantness (N = 61)

	Mean ± SE	Range
Affective touch		
Baseline itch VAS score	6.80 ± 0.16	3.00-9.00
2-min measurement itch VAS score	3.83 ± 0.29	0.00-8.50
4-min measurement itch VAS score	3.57 ± 0.29	0.00-8.00
6-min measurement itch VAS score	3.39 ± 0.32	0.00-9.00
8-min measurement itch VAS score	3.60 ± 0.32	0.00-9.00
10-min measurement itch VAS score	3.80 ± 0.34	0.00-9.00
12-min measurement itch VAS score	3.82 ± 0.35	0.00-9.00
14-min measurement itch VAS score	4.06 ± 0.33	0.00-9.00
16-min measurement itch VAS score	4.17 ± 0.35	0.00-9.00
18-min measurement itch VAS score	4.16 ± 0.35	0.00-9.00
20-min measurement itch VAS score	4.24 ± 0.38	0.00-9.00
Baseline pleasantness VAS score	6.82 ± 0.22	0.00-10.00
Non-Affective touch		
Baseline itch VAS score	6.75 ± 0.21	2.00-10.00
2-min measurement itch VAS score	4.00 ± 0.34	0.00-9.00
4-min measurement itch VAS score	4.24 ± 0.34	0.00-9.00
6-min measurement itch VAS score	4.37 ± 0.34	0.00-9.00
8-min measurement itch VAS score	4.22 ± 0.35	0.00-9.00
10-min measurement itch VAS score	4.40 ± 0.33	0.00-9.00
12-min measurement itch VAS score	4.41 ± 0.36	0.00-9.00
14-min measurement itch VAS score	4.34 ± 0.35	0.00-9.00
16-min measurement itch VAS score	4.56 ± 0.36	0.00-9.00
18-min measurement itch VAS score	4.77 ± 0.37	0.00-9.50
20-min measurement itch VAS score	4.77 ± 0.38	0.00-9.50
Baseline pleasantness VAS score	5.24 ± 0.23	1.00-9.00
PVAQ Score	37.25 ± 1.35	13-62
Difference score of VAS scores for itch	0.55 ± 0.24	-3.20-5.00
Difference score of VAS scores for pleasantness	-1.58 ± 0.31	-6.00-8.50

Data of **Table 3.1** are partly visualized in **Figures 3.2**, **3.3**.

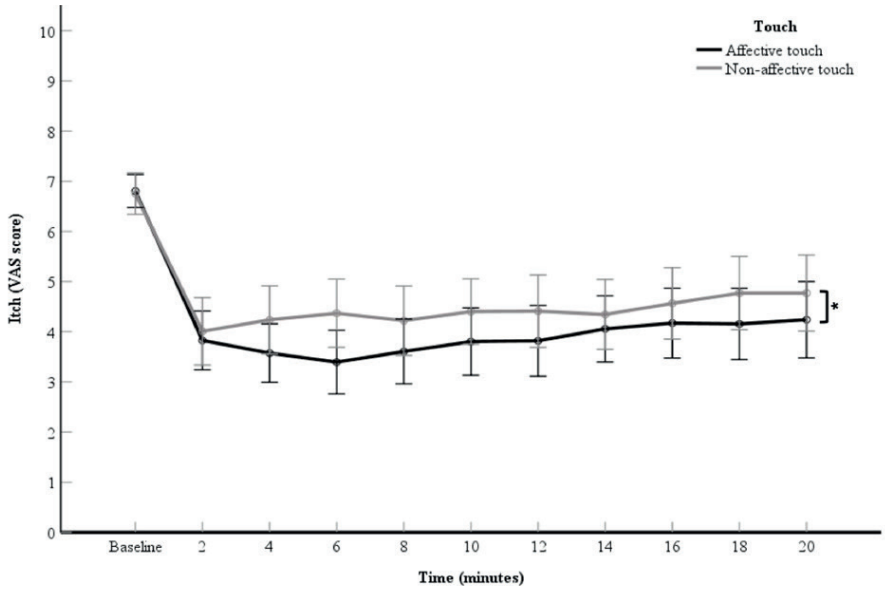

Figure 3.2. Mean of VAS scores for itch per 2 min itch measurement including the baseline measurement

The data points represent the means of the VAS scores for itch (with error bars depicting standard error). The black line represents affective touch and the gray line represents non-affective touch (N = 61). *p < 0.05; Displaying significant difference between type of touch.

Table 3.2. Results of the interaction effect between touch and itch, derived from a 2 × 10 repeated measures ANOVA contrast analysis

	Touch Time point	
Contrasts	***F***	***p***
2 vs. 4 min	4.66	0.035*
2 vs. 6 min	9.19	0.004**
2 vs. 8 min	2.14	0.148
2 vs. 10 min	1.31	0.257
2 vs. 12 min	1.25	0.268
2 vs. 14 min	0.08	0.773
2 vs. 16 min	0.34	0.564
2 vs. 18 min	1.29	0.261
2 vs. 20 min	0.78	0.380

For every contrast analysis, the degrees of freedom are 1.60.
$p < 0.05$. ** $p < 0.01$.

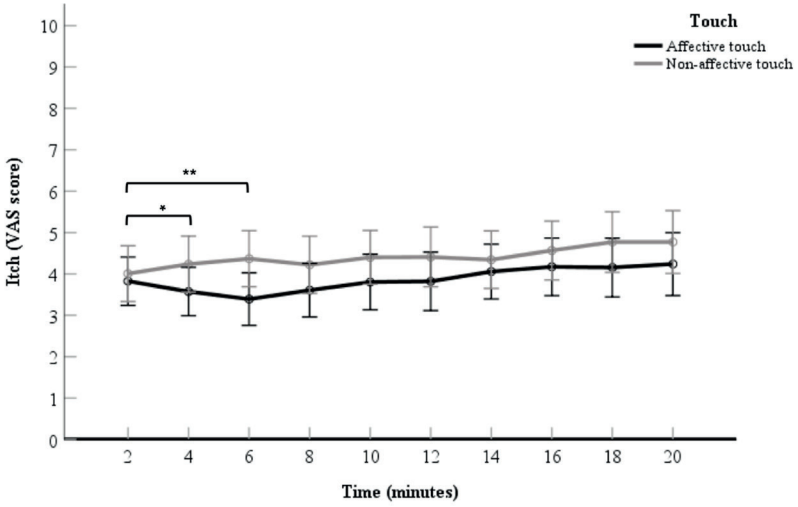

Figure 3.3. Mean of VAS scores for itch per 2 min itch measurement including the baseline measurement
The data points represent the mean of the VAS scores for itch (with error bars depicting standard error). The black line represents affective touch and the gray line represents non-affective touch (N = 61).

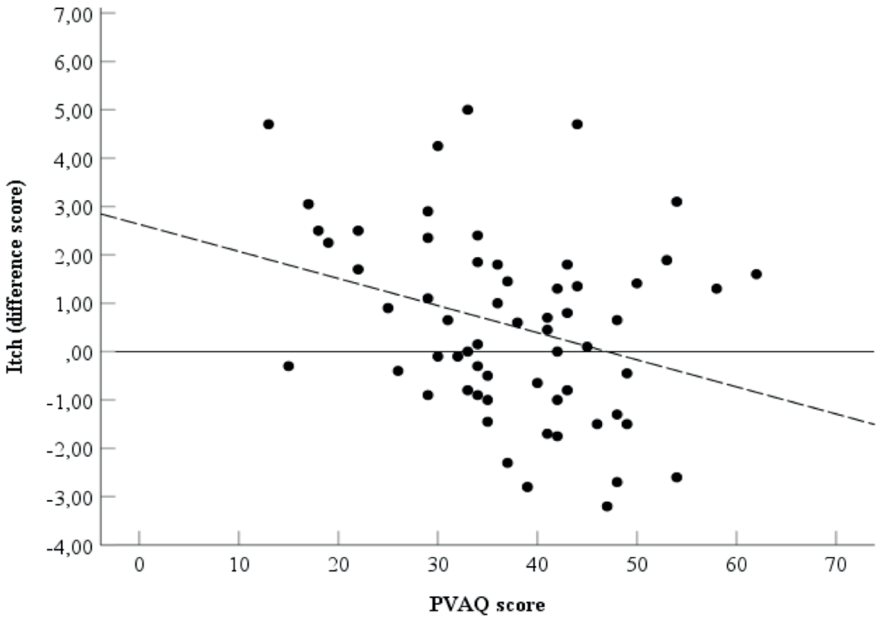

Figure 3.4. Relationship between PVAQ scores and itch. Spearman's ρ = −0.30
Black line represents point zero reference line. Dotted line represents the line of best fit.

3.3.3 Relieving Effect of Touch and Pleasantness

Spearman's correlation indicated no correlation between the difference in experienced pleasantness for affective and non-affective touch and the difference in itch ratings for the affective and non-affective touch conditions, ρ_s = -0.18, p = 0.17, two-tailed, N = 61.

3.3.4 Relieving Effect of Touch and PVAQ

Spearman's rho indicated the presence of a negative correlation between the PVAQ score (Table 3.1) and the relieving effect of affective touch, -0.30, p =0.02, two-tailed, N = 61 (Figure 3.4).

3.4. Discussion

Past studies revealed an inhibitory relationship between affective touch and pain and between pain and itch (Ikoma et al., 2003; Ikoma et al., 2006; Liljencrantz et al., 2017; Ständer & Schmelz, 2006). However, as far as we know, no research has been reported on the relationship between itch and affective touch. Therefore, this study investigated whether there is a relationship between itch and affective touch and in particular, whether affective touch inhibits itch.

The results showed that applying touch, either affective touch or non-affective touch, reduces itch experience. Several factors might account for this effect. First, it could be that the stroking of the arm is such a different sensation in comparison to electrically stimulated itch, that it is hard to feel both itch and stroking at the same time. Being touched might be a distraction on its own, independent of type of touch, which could explain why both types of touch reduced itch compared to baseline. On the other hand, there are studies showing that rubbing reliefs itch by activating low-threshold mechanosensitive A-fibers which inhibit itch signals in the spinal dorsal horn (Sakai et al., 2020; Yosipovitch et al., 2003). The velocity of rubbing could be compared to that of non-affective touch and might explain our findings. However, compared to rubbing, non-affective touch is applied with less force. This could influence the underlying mechanism regarding the inhibitory role on itch. Indeed, recent research in mice shows that a higher strength of stroking has a stronger inhibitory effect on itch. This implies that the strength of stroking plays an important role in itch inhibition (Sakai et al., 2020). Therefore, it may be unlikely that the decline in itch experience by non-affective touch in our study is based on the underlying mechanisms of rubbing.

Interestingly, affective touch had an additional relieving effect on itch experience compared to non-affective touch. These findings suggest that affective touch alleviates itch experience more than non-affective touch. This implies that affective touch interferes with the processing of itch, resulting in a reduction of itch experience. How affective touch exactly interferes with itch is not known yet, but answers may be found in recent research into the pleasurability of scratching (Bin Saif et al., 2012; Mochizuki et al., 2017; Mochizuki et al., 2014; Papoiu et al., 2013).

As described, when we feel itchy we tend to scratch the itchy site. In addition, scratching provides a pleasant and rewarding feeling which explains its addictive property (Papoiu et al., 2013). Scratching activates brain regions involved in the processing of pleasantness, affection and reward e.g. insula, ACC and prefrontal regions (Lloyd et al., 2015; Mochizuki et al., 2019; Mochizuki et al., 2014; Papoiu et al., 2013). The involvement of this pleasant reward network in the brain could represent a top-down mechanism initiating a decrease in itch experience (Hashimoto & Yosipovitch, 2019; Papoiu et al., 2013). Furthermore, the pleasurability of scratching is associated with inhibition of the insula and ACC, regions which are associated with the emotional and affective evaluation of itch (Papoiu et al., 2013). Interestingly, these regions are also involved in the processing of affective touch (McGlone et al., 2014). In addition, the pleasurability of scratching is mostly dependent on tactile sensations and it seems that on hairy parts of the body i.e. the arm or the back, CT-afferents are involved, which are also important for affective touch (Hashimoto & Yosipovitch, 2019; Mochizuki et al., 2017). Taken together, the overlap in brain regions involved in scratching and affective touch, the involvement of CT-afferents in the pleasurability of scratching and our results show that affective touch possibly modulates itch through activation of regions involved in pleasantness and reward resulting in a decrease in itch experience. To confirm, further research should focus on the underlying process of this inhibitory relationship, for example by measuring brain activity through EEG or fMRI.

In addition, the optimal duration of applying affective touch to experience a relieving effect was investigated. Based on Sailer et al. (2016), it was expected that the reduction in itch would persist for ~ 20 min. They stated that after 20 min, the brain areas activated by affective touch habituated to the stroking, which caused a decrease in brain activity and stabilized the experienced pleasantness of affective touch. Results of the current study showed that affective touch seems to reduce itch from 2 min after the start of appliance of affective touch and that this reduction in itch increased until 6 min after the start of stroking. After 6 min, this effect stabilized, but itch is still reduced compared to baseline. Importantly, even after 6 min, affective touch alleviated itch more than non-affective touch. The current

study reported different temporal effects in comparison to the study of Sailer et al. (2016), however they only researched the temporal effects of experienced pleasantness of affective touch and the accompanying brain activity. It could be that the temporal dynamics of the inhibitory effect of affective touch on itch do not depend on the perceived pleasantness of affective touch. Our results indeed show that the experienced pleasantness of affective touch does not correlate with the degree to which affective touch has a relieving effect on itch. This suggests that, even if affective touch is not experienced as pleasant, it still alleviates itch. This could be explained by CT-fiber activation and its possible independence of perceived pleasant, which is also hypothesized by Nagi et al. (2011).

In addition, this research contributes to the evidence for an influence of attentional focus on the experience of bodily sensations van Laarhoven et al. (2010) stated that a high attentional focus on bodily sensations is associated with a more intense experience of itch, suggesting that attention to bodily sensation does play a role in how much affective touch will relief itch. The results of the current study showed that higher attention to bodily sensations indeed mediated the experienced itch. Being more susceptible to experiencing bodily sensations can intensify the feeling of itch or will diminish the relief from affective touch, which is in agreement with the hypothesis.

The current study was not without limitations. First, different durations of the baseline itch measurement (4 s) and the experimental itch measurements (2 min) were used, limiting the comparability of the results. We also did not assess the time course of electrical stimulated itch experience over the 20 min period without stroking. Any habituation to the electrical stimulus could therefore not be taken into account. In further research, it is recommended to add an extra control condition in which itch experience over time is measured without tactile input.

Secondly, electrical stimulation as a way to induce itch has its limitation. It has been reported that not everybody experienced the electrical stimulation as itch (Yuan et al., 2016). An alternative way for future research to induce itch is using cowhage, a plant-based itch inducing substance evoking a mild itch (Andersen et al., 2017).

Thirdly, 80% of the participants was female. This imbalance could have influenced the results. A recent meta-analysis into affective touch shows that females perceive affective touch as more pleasant than men (Russo et al., 2020). Furthermore, research into sex difference and itch experience shows that women report higher itch intensities compared to men. However, there was no difference in reduction of itch intensity between men and women when distracted (Stumpf et al., 2013). As our results show that pleasantness does not correlate with the degree of itch reduction and itch reduction itself is not

influenced by gender, it may be unlikely that the skewed male/female ratio in our study influences the results. Nevertheless, the imbalance between male and female in our study should be taken into account when generalizing outcomes to the general population.

To expand fundamental knowledge on affective touch and its potential to contribute to clinical applications, future research should take individual differences into account. While some participants did not experience relief from affective touch, others reacted extremely well and experienced no itch at all after only two minutes of affective touch. These different responses could be caused by individual differences concerning tactile communication and touch perception (Harjunen et al., 2017). For example, Luong et al. (2017) suggest that people have a stable preferred velocity of affective touch. These findings propose that individuals might respond differently to affective touch and that stroking should be adjusted to their preferred velocity.

To summarize, the current study showed that affective touch has a relieving effect on electrical stimulated itch. The relieving effect of affective touch is noticeable 2 min after the affective stroking has started, it stabilizes after 6 min, but persists up to 20 min. In addition, this effect is independent of the experienced pleasantness of affective touch. Lastly, a higher awareness of bodily sensations interferes with the relieving effect of affective touch on itch. The current study can serve as groundwork for future research in the application of affective touch as therapy for patient groups who experience itch as a significant burden. For this, it is necessary to determine how individuals with different kinds of non-histaminergic itch respond to affective touch and which characteristics result in maximal itch relief.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Faculty Ethics Review Board, Faculty of Social Sciences, Utrecht University. The participants provided their written informed consent to participate in this study.

Author contributions

LM: concept, supervision, writing, and editing. ZS and KR: concept, data collection, and writing. HD: concept, supervision, and writing. All authors contributed to the article and approved the submitted version.

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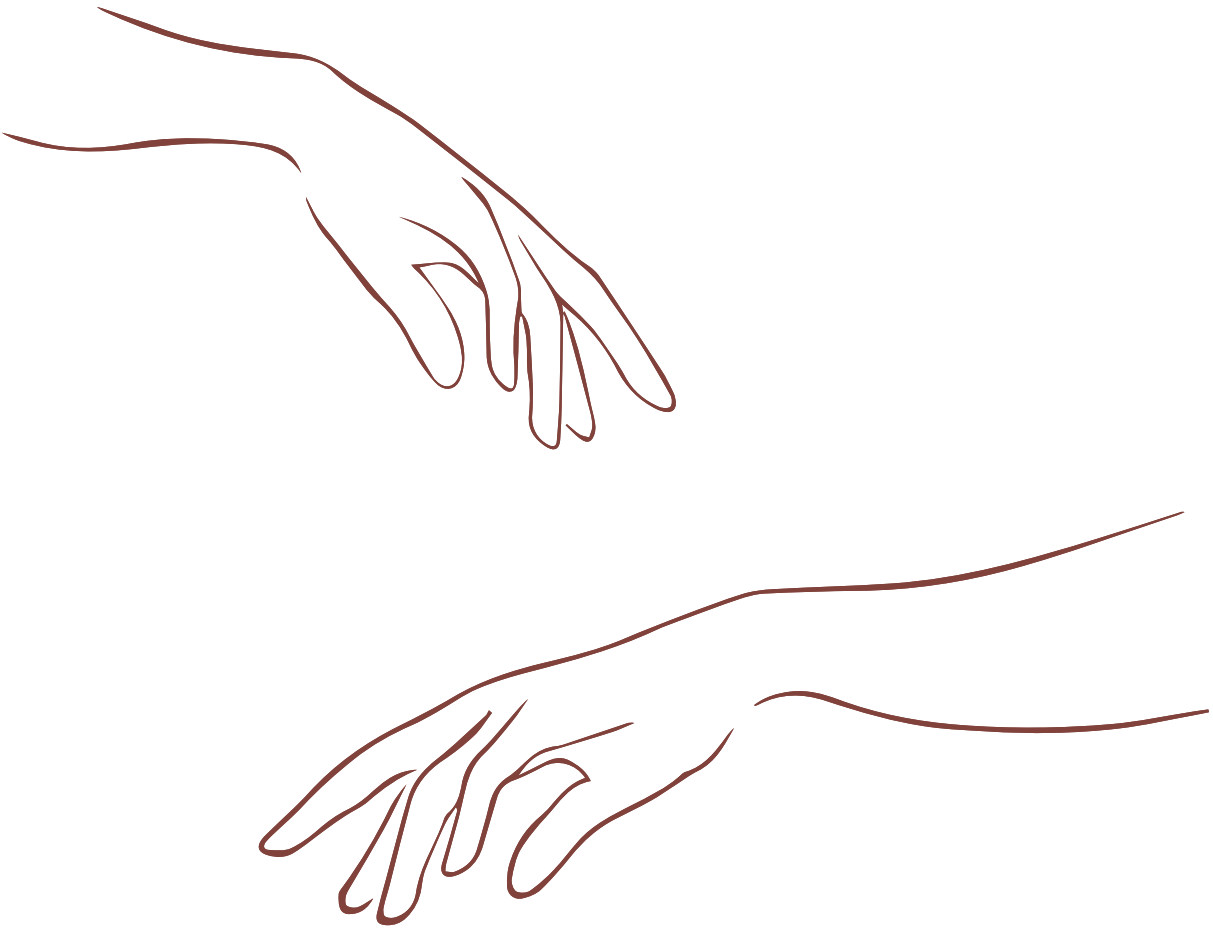
Chapter 4



Chronic pain relief after receiving affective touch; a single case study

Larissa L. Meijer
Carla Ruis
Maarten J. van der Smagt
H. Chris Dijkerman

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Abstract

Affective touch is gentle slow stroking of the skin, which can reduce experimentally induced pain. Our participant, suffering from Parkinson's Disease and chronic pain, received 1 week of non-affective touch and 1 week of affective touch as part of a larger study. Interestingly, after 2 days of receiving affective touch, the participant started to feel less pain. After 7 days, the burning painful sensations fully disappeared. This suggest that affective touch may reduce chronic pain in clinical populations.

Keywords: affective touch, chronic pain, Parkinson's disease

4.1. Introduction

Chronic pain (CP) is defined as ongoing disabling pain that lasts for at least 3 months or beyond its expected time for normal healing. As CP can have various underlying pathophysiological mechanisms it is difficult to find a suitable treatment (Anwar, 2016). Currently, CP treatment is based on a multimodal approach in which pharmacological, non-pharmacological and physical rehabilitation are combined. Unfortunately, these treatments are often insufficient (Bicket & Mao, 2015). Therefore, it is important to investigate new possible ways to reduce CP, of which affective touch (AT) seems a promising candidate.

Affective Touch is gentle slow stroking of the skin, applied at a speed of 1 – 10 cm/s (optimally 3 cm/s), that activates a particular type of nerve fibers (C-Tactile afferent: Björnsdotter et al., 2010). Research shows that AT and the underlying C-Tactile system can reduce experimentally induced pain (Meijer et al., 2022; von Mohr, Krahé, et al., 2018). However, only a few studies investigated the effect of AT in CP conditions (Di Lernia et al., 2020; Habig et al., 2021).

This single case study describes a man diagnosed with Parkinson's Disease (PD) in 2015 and suffering from CP since 2021. He reported enduring pain relief after receiving AT. This case is unique as it is, as far as we know, the first time the effect of AT on CP is investigated in a longitudinal design. Second, the participant's pain has fully disappeared after receiving AT, which has not been reported yet. Third, this effect persisted even after AT administration had stopped. Altogether, this case further emphasizes the pain-relieving effect AT might have.

4.2. Case report

The participant was a 73-year-old man, who first reported the CP symptoms to his General Practitioner (GP) in September 2021. At that time, the symptoms were reported as multiple generalized pain symptoms with an unknown cause. The GP subscribed Naproxen pain killers, paracetamol and/or ibuprofen which could be taken if necessary. However, the participant reported that these painkillers were insufficient and caused side effects, therefore he stopped taking this medication frequently. During the study the participant did not use any pain medication. Before the start of the study in May 2022, the participant reported pain in his knee and (lower) back. Additionally, he described a 'burning painful sensation' in both hands, where the pain was seemingly more on the

'surface of his skin'. There was no clear trigger for this pain, which was on and off present during the day and sometimes more prominent in one hand compared to the other. As the described burning pain could be a sign of neuropathic pain and therefore might influence touch perception or could even cause allodynia (Jones et al., 2003), before the start of the study the experimenter checked whether the participant could perceive touch and if touch did not elicit an unpleasant experience. The participant could perceive touch and described touch as 'definitely not unpleasant'. Based on this experience and that the participant has not been diagnosed with neuropathic pain, it was decided that the participant was eligible for participating in this study. As part of a larger study protocol, the participant registered his overall pain experience for one week which was used as a baseline measurement and to control for normally present pain fluctuation. Hereafter, he received one week of non-affective touch (non-AT) treatment followed by one week of AT treatment. The specific treatment order for this case was the result of the order being counter-balanced between participants of the larger study. Touch was applied by his partner, who received training which included several demonstrations of both types of touch, a written instruction sheet and a video. Halfway through the week and at the end of the touch week, the experimenter video called the partner and participant to control if touch applications were still done correctly. Touch was applied in the morning and the evening for 15 min on the forearm, in which left and right forearm were alternated between sessions. AT was applied with a speed of around 3 cm/s, which is similar to stroking from elbow to wrist in 6 s. Non-AT was applied with a speed of around 18 cm/s, which is similar to stroking from elbow to wrist in 1 s. Pain experience was measured by the Colour Analogue Scale for pain (CAS) and the Faces Pain Scale-Revised (FPS-R), both range from 0 ('no pain') to 10 ('severe pain'; Scherder & Bouma, 2000). In addition, the pleasantness of both types of touch was registered by a Visual Analogue Scale ranging from 0 ('unpleasant') to 10 ('pleasant'). Both types of touch were rated between 2-3, which can be interpreted as 'slightly unpleasant'. However, the participant described the sensation of both types of touch as 'neutral and not painful'. There was no significant difference in pleasantness between AT (M = 2.06, SD = .15) and non-AT (M = 2.63, SD = .71); $t(6) = -2.43$, $p = .051$.

During the non-AT treatment, the participant reported some changes in pain experience but no clear increase or decrease. After receiving AT for 1 day, the participant started to feel less pain. After 3 days the participant reported that the burning painful sensation in both his hands had 'fully disappeared', which persisted until the seventh day of the AT week (Figure 4.1; Table 4.1).

To determine whether these observed results were significant, the Nonoverlap of All Pairs (NAP) method was used. This is a single case analysis method which can be computed by the non-parametric Mann-Whitney U test (Morley, 2018; Parker et al., 2011). As this method can only compare two conditions, we used SPSS to conduct three analyses per questionnaire; no touch – AT, no touch – non-AT and AT – non-AT. There was a significant difference between the no touch and AT condition for both questionnaires. A significant difference between no touch and non-AT was only observed for the CAS but not for the FPS-R. However, the difference between non-AT and the no touch condition is much smaller than for AT and no touch. The standard deviation for non-AT is much larger than for AT (see Table 4.1), which reflects the fluctuation during the non-AT week as shown in Figure 4.1. Importantly, there was also a significant difference between the AT and non-AT condition (Table 4.2).

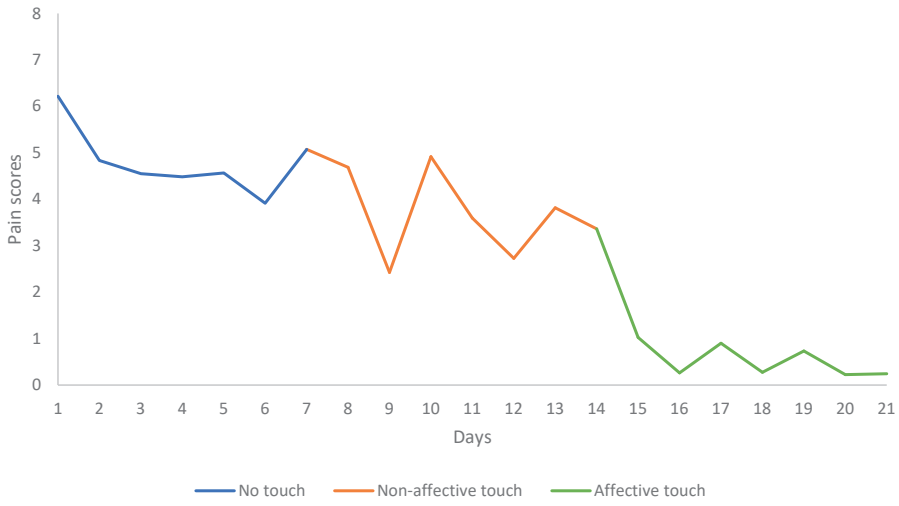

Figure 4.1. Representation of the participants pain experience at each day of the whole experimental cycle
Pain scores represent the combined means of the CAS and FPS-R.

Table 4.1. Mean and standard deviation of pain experience measured by the CAS and FPS-R

	CAS		FPS-R	
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**
No touch	5.18	.59	4.43	.88
Non-AT	3.74	.71	3.55	1.19
AT	.67	.22	.38	.49

Table 4.2. Results of Mann-Whitney U analysis

	CAS			FPS-R		
	M Rank	***Z***	***P****	***M Rank***	***z***	***P****
No touch – AT	11.00	-3.13	.003	11.00	-3.18	.003
	4.00			4.00		
No touch – non-AT	10.79	-2.95	.003	9.07	-1.42	.418
	4.21			5.93		
AT – non-AT	4.00	-3.14	.003	4.00	-3.17	.003
	11.00			11.00		

**Bonferonni corrected p*

At the moment of debriefing (2.5 weeks later) the participant subjectively reported that the burning pain was still gone from both his hands, even though they had stopped administering AT after completing the study protocol. The participant and his partner said 'we do not fully understand how this type of touch works but interestingly and somewhat surprisingly the pain is completely gone'. To see whether this pain-relieving effect of AT persisted, the participant was contacted 2 months later; he reported to 'feel no pain in his hands at all' since the end of the study and therefore felt no need to administer AT. The participant did not report any change in pain experience for his knee and lower back. However, the participants described the burning pain in his hands as the most disabling, and as AT effectively reduced this pain, the participant focused on this pain sensation during the experiment. As the follow-up was not part of the study protocol, this was only subjectively reported and not measured with the CAS or FPS-R.

4.3. Discussion

The results of this single case report are promising as this suggest that AT may reduce pain experience in clinical populations. This is in line with previous research in which CP and specifically neuropathic pain patients report pain relief while receiving AT (Di Lernia et al., 2020). However, this study made use of an experimental setting and touch was applied by a device. In our study touch is applied by the partner. This has already been reported to enhance the positive effect of AT on pain by von Mohr, Krahé, et al. (2018), but in an experimental setting targeting acute pain instead of CP. Our study provides novel insights as we use a treatment protocol and longitudinal design.

The results are in line with a recent model of Meijer et al. (2022), suggesting that AT interacts with pain processing pathways on different levels of the nervous system resulting in decreased pain experience. As mentioned, CP is caused by several pathophysiological mechanisms. Di Lernia et al. (2020) suggests that AT might be a form of pain analgesia modulating the parasympathetic system, μ-opioid system, oxytocin release and pain processing pathways as also proposed by Meijer et al. (2022). This interaction with several physiological mechanisms might explain its analgesic effect on CP.

However, the burning pain the participant reported could also be a sign of neuropathic pain. Specifically, as the pain was on and off present, described as a burning sensation and touch was experienced as slightly unpleasant, it could be caused by hyperexcitability of the spinal cord (Baron, 2000). As only the pain in the hand diminished, one could speculate that AT interacted with the pain processing more on the peripheral level of the spinal cord by altering the hyperexcitability (Meijer et al., 2022). A more peripheral role for AT is further underlined by the observation that, even though the participant did not perceive AT as pleasant, which is linked to oxytocin release and activation of the insula, it still relieves pain. This suggests that the pain-relieving effect of AT depends more on activity of the underlying C-tactile system than on the pleasant experience of this type of touch (Meijer et al., 2022; von Mohr, Krahé, et al., 2018).

In addition, this is the first study reporting that AT can not only relieve pain immediately, but that this effect persists after the AT application had stopped. Previous research shows that CP in PD is mostly caused by overactivation of the pain system (Antonini et al., 2018). Based on the model of Meijer et al. (2022), the reported persisting effect might suggest that AT modified the overactive pain system to its normal state resulting in permanent pain relief. Furthermore, Di Lernia et al. (2020) suggest that the interaction between AT and CP are

linked to interoception. It seems that interoceptive accuracy, that is the ability to correctly perceive the body, is lowered in CP which causes enhanced pain experience. AT, as interoceptive stimulation, might restore the ability to correctly perceive the body in CP.

In contrast, it seems that not only AT influenced pain experience, but non-AT did as well to a certain extent. Even though the participant subjectively did not report any change in pain experience during the non-AT week, at least on one of the questionnaires there is a significant difference with the no touch condition. It could be that being touched is a distraction from the pain. Furthermore, non-AT, as a faster touch more similar to rubbing, activates the Aβ fibers which also seems to interact with pain on a spinal cord level. However, this is linked to acute pain and reduces pain temporarily (Meijer et al., 2022). This might also explain the fluctuation in pain experience during the non-AT week. However, the significant difference between non-AT and AT further emphasizes that AT, besides a possible distraction from pain, has an additional pain-relieving effect which is persistent.

Overall, this case report shows that AT may be a promising new method to reduce CP in clinical populations. Naturally, as this is a single case report, further research in a larger clinical sample is warranted.

Author contributions

Larissa L. Meijer: Conceptualization; data curation; formal analysis; funding acquisition; methodology; visualization; writing –original draft; writing –review and editing. **Carla Ruis**: Conceptualization; methodology; supervision; writing –original draft; writing –review and editing. **Maarten J. van der Smagt**: Conceptualization; formal analysis; methodology; supervision; writing –original draft; writing –review and editing. **H. Chris Dijkerman**: Conceptualization; formal analysis; funding acquisition; methodology; supervision; writing –original draft; writing –review and editing.

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Conflict of interest statement

All authors declare no conflict of interest.

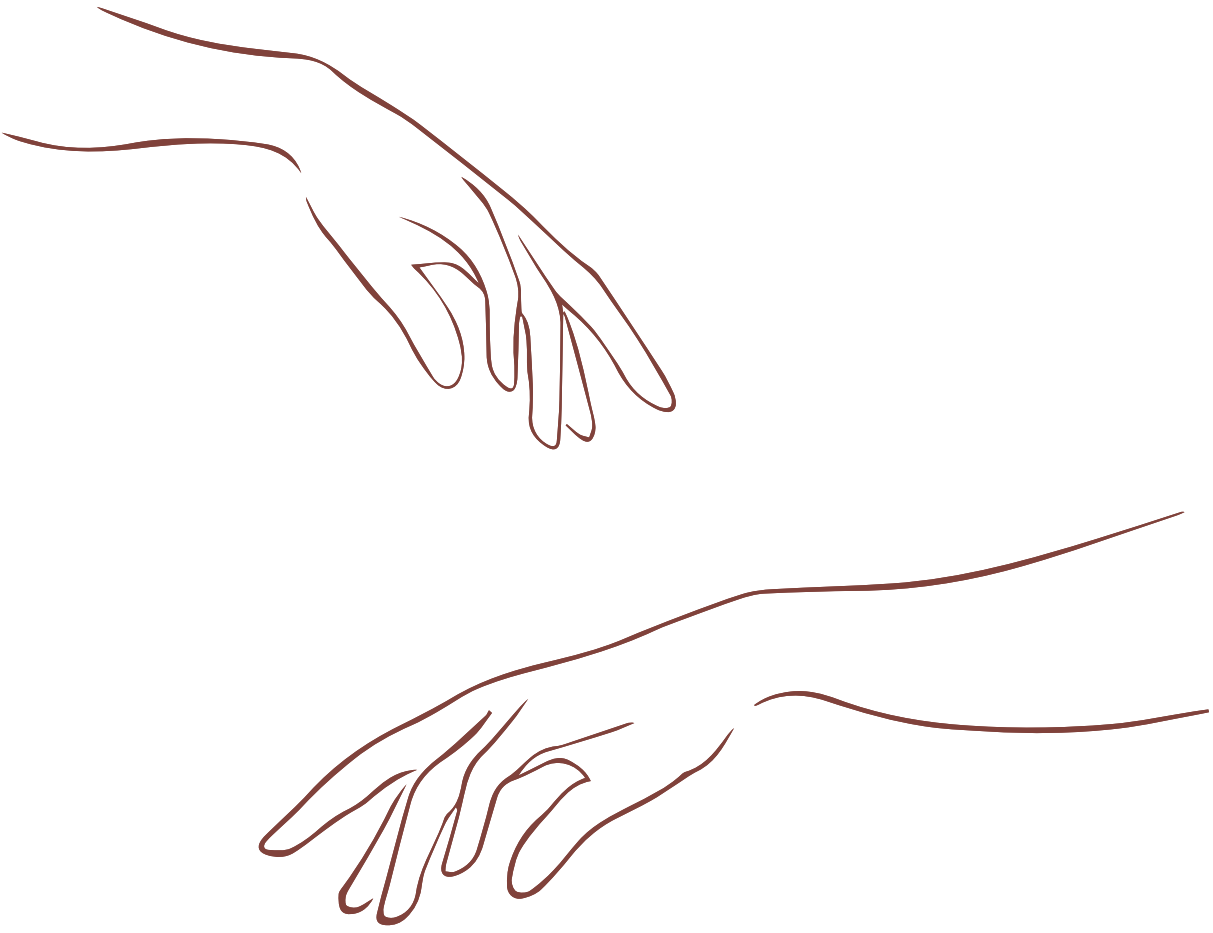
Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Informed consent

Our patient signed an informed consent form for publishing this data. The larger study, of which this single case study is part of, has been approved by the Medical Research Ethics Committee UMC Utrecht NL71563.041.20.

Chapter 5



CT-optimal touch and chronic pain experience in Parkinson's Disease; An intervention study

Larissa L. Meijer
Carla Ruis
Zoë A. Schielen
H. Chris Dijkerman
Maarten J. van der Smagt

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Abstract

One of the most underdiagnosed and undertreated non-motor symptoms of Parkinson's Disease is chronic pain. This is generally treated with analgesia which is not always effective and can cause several side-effects. Therefore, new ways to reduce chronic pain are needed. Several experimental studies show that affective touch can reduce acute pain. However, little is known about the effect of affective touch on chronic pain. The aim of the current study is to investigate whether affective touch can reduce the chronic pain experience in Parkinson patients. In this longitudinal study, 18 Parkinson patients underwent one week of pain registration, one week of affective touch and one week of non-affective touch. During each touch week, participants received touch from their partners twice a day for 15 min. Results show that both types of touch ameliorate the chronic pain experience. Furthermore, affective touch has an additional immediate relieving effect and is perceived as more pleasant. This study shows that affective touch can reduce the experienced chronic pain in Parkinson's Disease. As affective touch has an additional immediate relieving effect and is perceived as more pleasant than non-affective touch, we argue that it might be used when immediate pain relief is needed. Importantly, this study shows that affective touch can be administered by a partner and as a result is feasible to implement as daily routine.

Keywords

Affective touch, CT-optimal touch, Parkinson's Disease, Chronic pain

5.1. Introduction

In Parkinson's Disease (PD) 30-85% of the patients suffers from chronic pain, one of the most underdiagnosed and undertreated non-motor symptoms of PD (Buhmann et al., 2020; Edinoff et al., 2020; Marques & Brefel-Courbon, 2021). Chronic pain is defined as ongoing disabling pain which often results in reduced well-being and a lower quality of life (Leadley et al., 2014). The most commonly reported form of pain in PD is musculoskeletal, which is mostly treated by analgesics (Edinoff et al., 2020). However, analgesia can have several unpleasant side effects such as nausea, headaches, constipation, confusion and memory problems (Martel et al., 2015). Furthermore, PD patients who are treated with medication do not always report a decrease in discomfort (Rukavina et al., 2019). In order to develop novel interventions to reduce chronic pain in PD, it is important to understand its underlying mechanisms.

When a noxious stimulus innervates the skin (of healthy individuals), the pain signal is processed through two systems: the lateral and the medial pain system (Bell, 2018). The *lateral* system is involved in the sensory and discriminative aspects of pain, which represents the pain threshold (the minimum level at which a stimulus is perceived as painful: Woller et al., 2017). The *medial* system is crucial for the affective/motivational aspect of pain, which is associated with pain tolerance (the maximum level at which a pain stimulus is tolerated: Sewards & Sewards, 2002). In PD both the lateral and medial pain system appear to be overactive, which results in a lowered pain threshold and pain tolerance (Antonini et al., 2018; Rukavina et al., 2019; Zambito Marsala et al., 2011). This means that PD patients experience pain more severely than individuals without PD (Zambito Marsala et al., 2011). Moreover, research shows that not only central pain processing systems are disrupted, but that PD also causes changes in peripheral pain transmission (Buhmann et al., 2020; Rukavina et al., 2019). These changes in central and peripheral pain processing complicate current pain management (Antonini et al., 2018).

Interestingly, recent research suggests that affective touch might be a novel non-pharmacological alternative to alleviate pain. Affective touch is a gentle stroking of the skin, which activates the small unmyelinated C-Tactile (CT) afferent nerves (Björnsdotter et al., 2010). This tactile system can be activated by stroking between 1 – 10 cm/s, optimal speed is 3 cm/s, with a soft brush or hand, hence it is also referred to as CT-optimal touch (Björnsdotter et al., 2010; Morrison et al., 2011). Interestingly, recent behavioural research shows that CT-optimal touch can reduce pain experience in healthy individuals (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017). These behavioural findings can be explained by a novel

model suggesting that the CT-afferent system interacts with the medial pain system at different levels of the central nervous system (Meijer et al., 2022). In particular, it may inhibit pain signals at the level of the dorsal horn of the spinal cord and as a consequence prevent higher order processing of the pain signal (Lu & Perl, 2003). In addition, it may downregulate several cortical areas such as the insula and anterior cingulate cortex, which are important for the subjective appreciation of pain (Gursul et al., 2018; Krahé et al., 2016; von Mohr, Krahé, et al., 2018).

However, the above mentioned studies have focused on acute pain experience in an experimental setting including healthy individuals. Currently, little is known about the effect of CT-optimal touch in people suffering from chronic pain (Fusaro et al., 2022). One study shows that after 11 min of CT-optimal touch, chronic pain significantly reduced in patients suffering from primary chronic pain, secondary musculoskeletal pain and neuropathic pain (Di Lernia et al., 2020). As the majority of PD patients suffer from musculoskeletal pain, CT-optimal touch might reduce chronic pain in PD patients as well.

In the current 3-week longitudinal intervention study, participants diagnosed with PD and suffering from chronic pain report their pain experience before the intervention and during a CT-optimal touch *as well as* a CT non-optimal touch intervention. Based on previous studies we hypothesize that CT-optimal touch may reduce chronic pain in PD patients, and to a larger extent than CT non-optimal touch. Touch will be administered by the partner, as this enhances the positive effect of CT-optimal touch on pain (von Mohr, Krahé, et al., 2018). We can hereby also explore whether implementing CT-optimal touch in daily life and longitudinal administration is feasible. In addition to the effect of CT-optimal touch on chronic pain, the pleasantness of this type of touch will also be recorded. Based on the study of Kass-Iliyya et al. (2017), which investigated CT-optimal touch perception in Parkinson patients, we expect that CT-optimal touch is perceived as more pleasant than CT non-optimal touch. Furthermore, we will investigate whether there is a relationship between pleasantness ratings and the relieving effect of CT-optimal touch. If so, this might indicate that the pain relieving effect is merely related to having a concurrent pleasant sensation, rather than the specific activation of the CT-system. However, previous studies of von Mohr, Krahé, et al. (2018) and Meijer et al. (2021) into the effect CT-optimal touch on respectively acute pain and itch have failed to show such a relationship between the perceived pleasantness of CT-optimal touch and its relieving effect, suggesting it is not the experienced pleasantness per se that causes the pain reduction. Finally, if CT-optimal touch can ameliorate pain this might also positively influence mood and affect (McWilliams et al., 2003).

5.2. Materials and Methods

5.2.1 Participants

Participants who experience chronic pain and suffer from PD were recruited through ParkinsonNEXT, an online platform connecting researchers with aspiring participants diagnosed with PD (https://www.parkinsonnext.nl). Recruitment took place from September 2020 until December 2022. A total of 57 participants signed up for the study of which 31 were eligible for participation. Inclusion criteria were; age ≥18, PD diagnosis, pain associated with PD (musculoskeletal, dystonic, akathisia) and/or pain worsened by PD (i.e. (osteo) arthritis, other age-related pain conditions), pain present for at least 3 months, with clear impact on physical/psychological functioning (measured with the King's Parkinson's Disease Pain Scale), which must be assessed as at least moderate in intensity (≥4 points on an 11-point Likert pain scale) and the ability to provide informed consent. Exclusion criteria were incapability of giving informed consent, inability to understand questionnaires, suffering from conditions that affect the ability to feel or process touch, pain conditions that can also influence the perception and processing of touch; i.e. neuropathic pain, a history of cerebral traumata or psychiatric disorders unrelated to PD and currently suffering from a mood disorder. During the study 12 participants dropped out because; during the first week of the study they did not report to experience pain (N=4); it was too difficult to combine this 3-week intervention with their daily-working-schedules (N=5); partner was not able to provide touch frequently due to physical limitations (N=2). One participant dropped out because of a painful sensation elicited by CT non-optimal touch. As a result, 19 participants (8 women), aged between 31 and 76 years (M=65.47, SD=11.22) and mostly suffering from musculoskeletal pain successfully participated in the study (for more descriptives see Table A1. in the Appendix). One additional participant was excluded from the sample, as the origin of his pain and study outcome were very different from the other participants in this study. The results of this participant are reported in a single case report (Meijer et al., 2023). Thus, data of 18 participants was used for the analyses. All participants provided written informed consent, which were stored separately from all anonymized data. The study was performed in agreement with the WMA Declaration of Helsinki 2013 and has been approved by the medical research ethics committee at the UMC Utrecht (NL71563.041.20).

5.2.2 Materials and measures

Several questionnaires were administered before and during the study. The questionnaires are categorized based on the moment of administration.

5.2.2.1 Before the start of the study

Pain intensity: The Pain Intensity Scale (PIS) was used to measure the intensity of the experienced chronic pain at that particular moment; the participant filled out a 11-point Likert pain scale for pain intensity. A score of <4 points was used as an exclusion criteria.

Chronic pain: The participants' chronic pain experience was measured using the Kings Parkinson's Disease Pain Scale (KPDPS). This was used as a baseline pain measurement. The KPDPS measures the intensity and severity of pain as well as localization and its relationship with motor fluctuations or musculoskeletal pain. This is an interviewer based questionnaire with 7 domains which are based on common types of chronic pain in Parkinson patients. The total score is the sum of all domains, which are based on the severity multiplied by frequency (Chaudhuri et al., 2015).

Cognition: To assess whether participants were able to provide informed consent the Montreal Cognitive Assessment (MoCa) or Telephone Interview for Cognitive status Modified (TICS-M) was administered. Research shows that in PD patients, the MoCa can detect the likelihood of impaired cognitive capacity in which a cut-off score of ≤22 is most sensitive (94%) (Karlawish et al., 2013). As face-to-face testing was not always feasible due to the COVID-19 pandemic, the TICS-M was also used to assess the ability to provide informed consent. The TICS reflects general cognitive ability and can detect cognitive impairments, a cut-off score of <34 was used as this might indicate mild cognitive impairment (van den Berg et al., 2012).

Quality of relationship: As the partner of the participant provided touch during the study, we wanted to check whether there was no discrepancy between perceived quality of the relationship of the participant and their partner, as this might influence the way touch was applied and/or how touch was perceived. The quality of the relationship in terms of perceived support of the participant and partner was assessed through the Quality of Relationships Inventory (QRI) short form (Brier et al., 2018).

5.2.2.2 During the study

Pain intensity: The Color Analogue Scale (CAS) was used to measure pain *intensity*. The CAS is a questionnaire that measures pain intensity by using different colors: the white colored bottom represents 'no pain' and the dark red top represents 'extreme pain' (see Figure 5.1). These colors are linked to

a numeric scale from 0 – 10 which is not visible for the participant (Scherder & Bouma, 2000). In this study the CAS was used digitally (computer, phone or tablet) by clicking with a mouse or finger (touch screen) on a point in the scale which represent the current pain intensity.

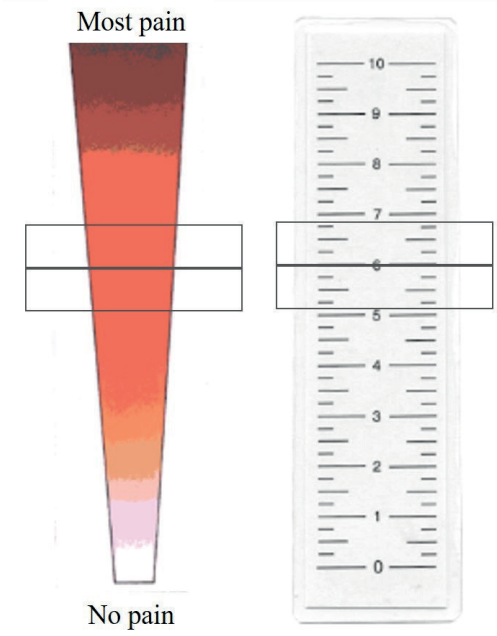

Figure 5.1. Color Analogue Scale. Adapated from (McGrath et al., 1996).

Pain severity: The Faces Pain Scale-Revised (FPS-R) was used to measure the *severity* of pain and the affective component. The FPS-R that contains six faces, on the left a neutral face and moving to the right five faces which express increasing feelings of pain (see Figure 5.2). The neutral face represent 0 'no pain' and the five painful faces represent an ascending score of 2, 4, 6, 8, 10 of which the latter represent 'severe pain' (Carrie L. Hicks et al., 2001; Scherder & Bouma, 2000; Ware et al., 2006). The FPS-R was used digitally by clicking (or touching) on the face representing the participants pain severity.

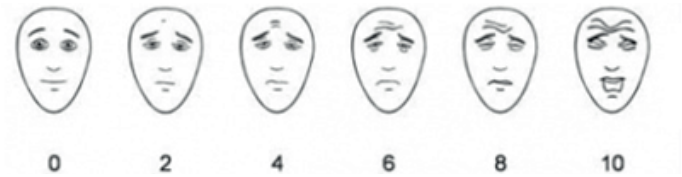

Figure 5.2. Faces Pain Scale-Revised. Adapted from (C. L. Hicks et al., 2001).

Pleasantness: The pleasantness of both types of touch was registered by a Visual Analogue Scale (VAS) ranging from 0 – 10, in which 0 represented 'unpleasant' and 10 'pleasant'.

Mood/affect: To assess the two dimensions of mood, namely positive- and negative affect, the Positive and Negative Affect Scale (PANAS) was used. This is a 20-item questionnaire, which has been shown to be a reliable, valid and efficient measure for positive- and negative affect (Watson et al., 1988). The PANAS was provided before (day 1)- and after (day 7) each touch intervention week, to measure if touch also influenced the participants affect in general.

Other: Participants received a diary in which relevant information could be reported, this included usage of pain medication, changes in daily activities which might influence pain and changes in quality of sleep.

5.2.2.3 Tactile stimulation

Two types of touch were administered to the participant. CT-optimal touch was administered by the participant's partner by stroking the forearm of the participant with the hand at a slow but natural speed of around 3 cm/s. This was done by moving from elbow to wrist in approximately 6 s. As a control condition CT non-optimal touch was administered by stroking the forearm at a faster but still natural speed of around 18 cm/s. This was done by moving from elbow to wrist in approximately 1 s. Partners received a demonstration and an instruction sheet on how to apply the type of touch. In addition, they also received a video in which the touch was demonstrated so they were able to look back and consult the demonstration at any time.

5.2.3 Design

This was a 3-week intervention study with a within-subjects design which included a baseline condition ('no touch' week) and two experimental conditions (CT-optimal touch and CT non-optimal touch). The order of the experimental conditions was counterbalanced across participants. The primary outcome measure was the subjective pain experience measured with the CAS and FPS-R.

5.2.4 Procedure

After an aspiring participant signed up through ParkinsonNEXT, contact information was sent to the experimenter. When a participant was interested in participating, had read the information letter and met the inclusion criteria, the experimenter made an appointment. During the first appointment the experimenter provided information regarding the procedure, the MoCa/TICS and PIS were filled out, informed consent was given and hereafter the KPDPS and QRI were filled out. Hereafter, the experimenter demonstrated the two types of touch and asked the partner to perform them so the experimenter could check whether the instructions were clear. The experienced pleasantness of both types of touch was also measured by asking to rate touch on a scale from 0 to 10, to control for possible unpleasant sensations elicited by either type of touch.

During the study, all participants partook in the following sequence: one week of pain registrations only (no-touch), one week of CT-optimal touch (and pain registrations) and one week of CT non-optimal touch (and pain registrations) (see Figure 5.3. for a timeline of the procedure). The order of touch-type was randomized between participants. All data was anonymised, coded and stored separately from the consent forms. Upon completion of the experiment, or when participants preliminary withdrew from the experiment, they were debriefed.

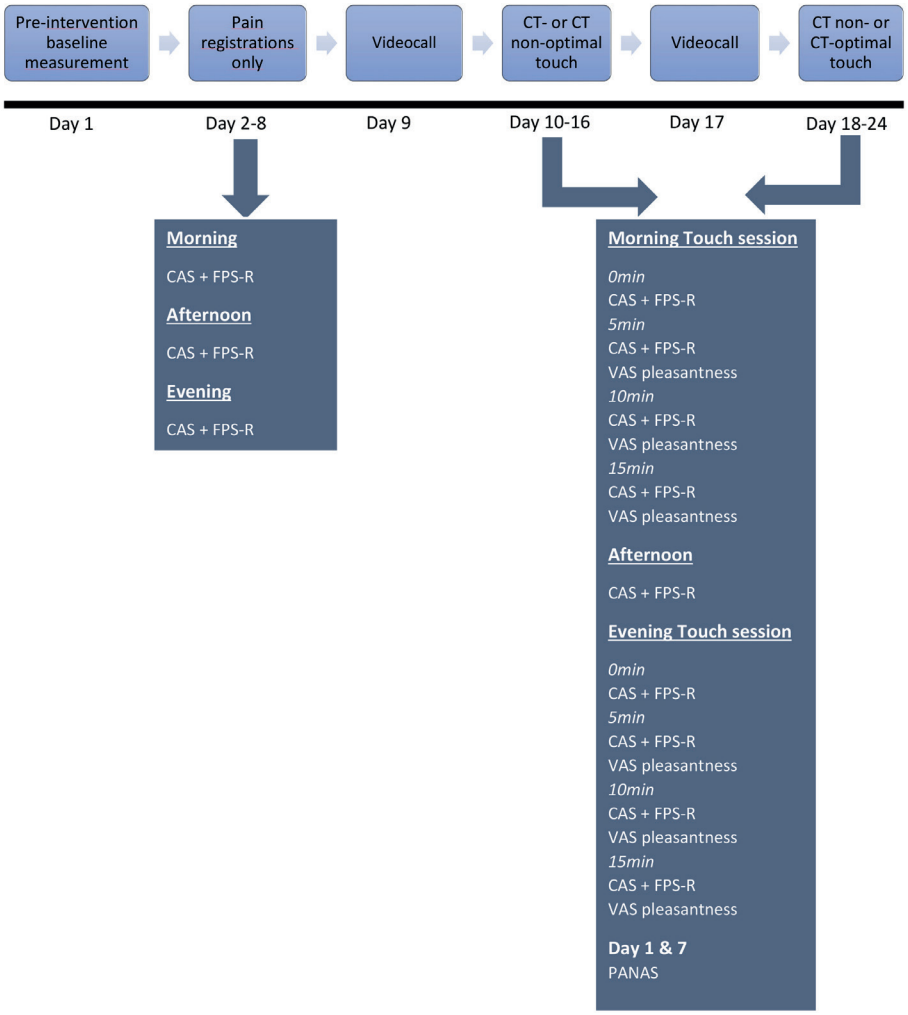

Figure 5.3. **Timeline of the intervention**

One week of pain registrations only/ 'no touch' week

Starting the day after the pre-intervention baseline measurement, participants reported their pain experience, measured by the CAS and the FPS-R, three times a day for one week to control for normally present pain fluctuation. The questionnaires were provided by Gorilla Experiment Builder (www.gorilla.sc), a survey tool. Two participants were not able to use Gorilla and were therefore provided with a hardcopy of the questionnaires.

One week of CT-optimal touch/CT non-optimal touch

The procedure for both touch weeks was identical. Before the start of the touch week the experimenter video-called the participant, during which the type of touch was demonstrated again and the procedure was explained. The next day the participant and partner started with one week of touch stimulation. Touch was administered twice a day (morning and evening, 15 min) by the partner of the patient. Pain ratings (CAS Pain Scale and FPS-R) were measured before, during (at 5 and 10 min) and after the stimulation (at 15 min). Partners kept track of time by using a (stop)watch. In addition, the pleasantness of the stimulation was also measured during (every 5 min) touch stimulation with the VAS pleasantness. To assess whether there were any long(er) term effects of touch stimulation during the day, pain ratings (CAS Pain Scale and FPS-R) were also measured in the afternoon. Half way through the week, the experimenter video called the participant and partner to ensure uniform touch administration. The partner was asked to perform the touch without any prior instruction, so that the experimenter could check whether touch was still applied correctly. This call was recorded, anonymized and touch performance of most of the participants was also checked by the other research team members. On the first and last day of the touch week participants filled out the PANAS.

5.2.5 Statistical analysis

All data was processed using Microsoft Excel (version 2208) and analyzed with SPSS Statistics (version 28), for more detailed information on data processing see the Appendix. Due to technical problems some participants unfortunately had trouble with reporting their pain experience in Gorilla, especially with the CAS Pain Scale. Therefore, the data of the CAS Pain Scale was deemed invalid and excluded from analyses.

The FPS-R data was normally distributed and sphericity was not violated. As we do not know from previous studies when and how possible pain reduction through CT-optimal touch compared to CT non-optimal touch may occur, several analyses were done. First, to analyze the difference in pain experience

over the week, the average FPS-R score of the three different conditions; no touch (NT), CT-optimal touch and CT non-optimal touch were analyzed with a repeated measures ANOVA. This is also referred to as the *overall-effect*. A Bonferroni post-hoc comparison was used to analyze the difference between the three conditions. Second, the average FPS-R score measured during touch administration (0 min to 15 min) were used to analyze whether the pain experience was more ameliorated by CT-optimal touch compared to CT non-optimal touch, referred to as the *short-term effect*. Here, paired t-tests were used to analyze the data. As we expected that CT-optimal touch ameliorated pain experience more than CT non-optimal touch, an one-tailed $p<.05$ was considered significant. Third, to analyze the optimal touch duration the average FPS-R scores on 0 min, 5 min, 10 min and 15 min were used. A touch x time repeated measures ANOVA was used to analyze the optimal duration of touch administration. Fourth, the average VAS pleasantness scores of both types of touch was analyzed with a Wilcoxon Signed Ranked test as this data was not normally distributed. Fifth, the PANAS score of both types of touch was analyzed with a touch x affect x day repeated measures ANOVA. Finally, a Spearman correlation was used to analyze the relation between the short-term FPS-R scores and VAS pleasantness.

5.3. Results

Before the start of the study participants' average PIS was 5.94 (SD=1.55) and for the KPDPS the average score was 37.06 (SD=15.55). The participants' total score on the QRI was 16.12 (SD=1.91) and the partner's score was 15.24 (1.83), this difference was not significant $t(16)=1.63$, $p=.123$. A support scale score and conflict score were also calculated (see Table A1 in the Appendix), here participants and their partners scored high on support and low on conflict (adapted from Brier et al. (2018). Taken together, we assumed that the quality of their relationship did not influence touch perception. The information reported in the diary was checked by the experimenter after participants finished the study. No changes or particularities were reported. To provide a clear-overview of the collected data and used analyses, outcomes are described as: the overall-effect, short-term effect including optimal touch duration, pleasantness, PANAS and relationship between pleasantness and short-term effect.

5.3.1 Overall- effect

The average FPS-R pain scores for the three conditions NT, CT- optimal touch and CT non-optimal touch were analyzed with a repeated measures ANOVA, which showed a significant effect of condition $F(2,34)=14.33$, $p<.001$, partial $\eta^2=.46$. A Bonferroni corrected post-hoc comparison showed a significant effect between NT – CT-optimal touch ($p<.001$) and NT – CT non-optimal touch ($p=.001$). There was no significant difference between CT-optimal touch – CT non-optimal touch ($p=1.00$). Thus, the FPS-R scores were significantly lower for the CT-optimal touch and CT non-optimal touch conditions compared to the no-touch condition (see Table 5.1. and Figure 5.4).

Table 5.1. Mean pain scores on the FPS-R per condition over the week

	Mean pain score	SD	N
No touch	4.27	1.21	18
CT-optimal touch	3.29	1.18	18
CT non-optimal touch	3.25	1.28	18

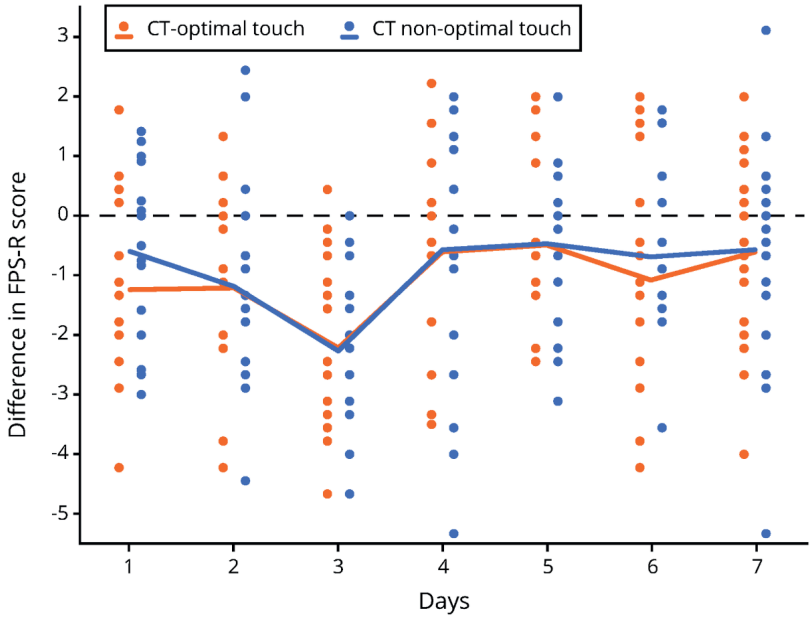

Figure 5.4. Scatterplot depicting FPS-R difference scores per day for CT-optimal touch – NT and CT non-optimal touch – NT. The dots represent individual datapoints, the lines show the sample mean.

As the type of touch was counterbalanced between participants, the data was checked for a possible order effect. For the FPS-R scores a difference score was calculated by subtracting the CT-optimal touch and CT non-optimal touch week from the NT week. A touch (2 levels) x order (2 levels) repeated measures ANOVA was used to analyze the data. There was no significant difference between NT – CT-optimal touch and NT – CT non-optimal touch over the week $F(1,16)=.14$, $p=.713$. There was also no significant interaction effect between touch x order $F(1,16)=.01$, $p=.945$. Note, that the F-values here are very low which indicates a low probability of a significant difference. However, this might be explained by a lack of power, as the between-subject factor order consisted of two groups, one starting with CT-optimal touch (N=9) and one starting with CT non-optimal touch (N=9).

5.3.2 Short-term effect

To analyze the immediate effect of touch on pain experience, first FPS-R difference scores between the different timepoints (0, 5, 10, 15 min) were calculated (see Table 5.2). As described, as it is expected that CT-optimal touch ameliorated pain experience more than CT non-optimal touch, an one-tailed $p<.05$ was considered significant.

Table 5.2. Mean (SD) FPS-R difference scores between different timepoints for CT-optimal touch and CT non-optimal touch

	5 min – 0 min	**10 min – 0 min**	**15 min – 0 min**
CT-optimal touch	-.30 (.42)	-.57 (.50)	-.74 (.62)
CT non-optimal touch	-.24 (.24)	-.45 (.38)	-.49 (.40)

A t-test showed a significant difference between CT-optimal touch and CT non-optimal touch for 15 min – 0 min, $t(17)= -2.11$, $p=.025$, Cohen's $d=.52$. In other words, the pain alleviation effect is significantly larger for CT-optimal touch than for CT non-optimal touch. There is no significant difference between CT-optimal touch and CT non-optimal touch for 10 min – 0 min, $t(17)=-1.16$, $p=.130$ and for 5 min – 0 min, $t(17)=-.57$, $p=.290$.

We also analyzed whether this immediate effect of CT-optimal touch lasted after stopping administration. We compared the afternoon FPS-R scores, when touch was not administered, with the morning FPS-R scores. An average afternoon week score was calculated for both CT-optimal touch and CT non-optimal touch and this was also done for the 0 min morning timepoint (before touch administration) (see Table 5.3).

Table 5.3. Mean (SD) FPS-R week scores for the afternoon and 0 min morning time-point for CT-optimal touch and CT non-optimal touch

	Afternoon	0 min morning
CT-optimal touch	3.63 (1.46)	3.57 (1.10)
CT non-optimal touch	3.56 (1.48)	3.51 (1.36)

These scores were analyzed with a touch (2 levels) x time (2 levels) repeated measures ANOVA, which showed no significant effect for type of touch $F(1,17)=.09$, $p=.759$, no significant effect for time $F(1,17)=.07$, $p=.798$ and there was also no significant interaction between touch x time $F(1,17)=.00$, $p=.992$.

Since the pain amelioration is larger for CT-optimal touch than for CT non-optimal touch during touch administration, the optimal duration of applying touch was also analyzed. The average FPS-R score for CT-optimal touch and CT non-optimal touch was calculated for every timepoint (see Table 5.4).

Table 5.4. FPS-R scores (mean (SD)) for CT-optimal touch and CT non-optimal touch for the different timepoints

	CT-optimal touch	CT non-optimal touch
0 min	3.65 (1.15)	3.52 (1.27)
5 min	3.36 (1.18)	3.28 (1.35)
10 min	3.06 (1.24)	3.06 (1.22)
15 min	2.91 (1.23)	3.03 (1.27)

A touch (2 levels) x time (4 levels) repeated measures ANOVA was done to analyze the difference between timepoints for CT-optimal touch and CT non-optimal touch. There was no significant effect for type of touch $F(1,17)=.01$, $p=.910$. There was a significant effect for time $F(3,51)=27.22$, $p<.001$, partial $\eta^2=.62$. There was also a significant interaction between touch x time $F(3,51)=2.90$, $p=.044$, partial $\eta^2=.15$. A Bonferroni corrected post-hoc comparison was used to analyze the difference between time-points for CT-optimal touch and CT non-optimal touch. For CT-optimal touch there is a significant difference between 10 min – 0 min ($p<.001$), 15 min – 0 min ($p<.001$), 10 min – 5 min ($p=.001$) and 15 min – 5 min ($p<.001$), but not between 5 min – 0 min ($p=.051$) and 15 min – 10 min ($p=.081$). For CT non-optimal touch there is a significant difference between 5 min – 0 min ($p=.004$), 10 min – 0 min ($p<.001$), 15 min – 0 min ($p<.001$), 10 min – 5 min ($p=.030$) and 15 min – 5 min ($p=.022$), but not between and 15 min – 10 min ($p=1.00$) (see Table A2 in the Appendix).

5.3.3 Pleasantness

The difference in VAS pleasantness scores for CT-optimal touch and CT non-optimal touch were analyzed with a Wilcoxon Signed Ranked test as a data was not normally distributed. The VAS pleasantness score was significantly higher for CT-optimal touch, Wilcoxon ranked Z=-3.78, p<.001, r=.80 (see Table 5.5).

Table 5.5. Mean pleasantness scores for CT-optimal touch and CT non-optimal touch over the week

	Mean pleasantness	SD	N
CT-optimal touch	7.81	1.89	18
CT non-optimal touch	6.30	1.76	18

5.3.4 PANAS

The PANAS scores at day 1 and day 7 were used to analyze if there is a difference in positive or negative affect during the CT-optimal touch and CT non-optimal touch condition (see Table 5.6). Several participants did not fill out (parts of) the PANAS due to technical difficulties, therefore N=14. A touch (2 levels) x Positive or negative affect (2 levels) x day (2 levels) ANOVA was used to analyze the data. There was no significant effect for touch F(1,13)=.37, p=.555, day F(1,13)=.03, p=. 867 and there was also no significant interaction between touch x day F(1,13)=.05, p=.829. As there is no significant difference in the PANAS scores further analysis has not been executed.

Table 5.6. The mean (SD) PANAS scores for the positive and negative affect scale on day 1 and 7

	Positive affect *Day 1*	Positive affect *Day 7*	Negative affect *Day 1*	Negative affect *Day 7*
CT-optimal touch	26.79 (7.23)	27.86 (8.21)	17.14 (6.72)	16.29 (4.83)
CT non-optimal touch	27.36 (7.30)	26.57 (7.28)	17.57 (7.05)	17.79 (7.18)

5.3.5 Pleasantness and short-term effect CT-optimal touch

To analyze whether the short-term effect of CT-optimal touch may be related to the perceived pleasantness of this type of touch, a Spearman correlation was used. No significant correlation was apparent between the short-term effect of CT-optimal touch and its perceived pleasantness, ρ= -0.32, p=.201.

5.4. Discussion

Previous studies have shown that CT-optimal touch can reduce acute pain in an experimental setting (Habig et al., 2017; Krahé et al., 2016; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018). However, only little is known about the effect of CT-optimal touch on chronic pain and this was tested in an experimental setting (Di Lernia et al., 2020; Fusaro et al., 2022). As PD patients are known to suffer severely from chronic pain and currently effective treatment is missing (Rukavina et al., 2019), the aim of the current study was to investigate the influence of CT-optimal touch on chronic pain experience in PD in a non-experimental setting. By doing so, the feasibility of CT-optimal touch application by a partner in daily life could also be explored.

As this is, as far as we know, the first longitudinal study into the effects of CT-optimal touch on chronic pain in PD, several analyses were conducted to investigate if and when pain amelioration occurs. The results show that both types of touch significantly reduce experienced chronic pain over the week. That is, both CT-optimal touch and CT non-optimal touch are effective in reducing the chronic pain experience in PD, and the order of the touch condition did not influence this result. In addition to the overall-effect, an immediate effect of touch on chronic pain experience was also investigated. Here, the results showed that CT-optimal touch reduces the chronic pain experience significantly more compared to CT non-optimal touch. Furthermore, CT-optimal touch appears to be most effective after at least 10 to 15 min.

The current results show that over the week, CT non-optimal touch may be as effective in reducing chronic pain as CT-optimal touch. Based on the study of Di Lernia et al. (2020) and the underlying mechanisms of both types of touch, this was unexpected. However, in the study of Di Lernia et al. (2020) the control condition was touch vibration applied by a device instead of CT non-optimal touch applied by a partner. CT non-optimal touch is a faster touch which is naturally applied with more force than CT-optimal touch, most likely activating the Aβ-fibers (McGlone et al., 2014; von Mohr, Krahé, et al., 2018). From previous research it is known that the Aβ-fibers interact with pain on the level of the spinal cord. This is also referred to as the gate-control theory, which however has been criticized and might not fully explain the effect of CT non-optimal touch in the current study (Moayedi & Davis, 2013). Interestingly, as touch has been applied by the partner, the social component underlying touch might have added to the pain reducing effect of CT non-optimal touch, similar to the pain reducing effect that can be observed as a result of handholding, which also appears to rely mostly on the Aβ-fibers (Reddan et al., 2020). Receiving

social touch, such as caressing, handholding and massages has also been shown to have a positive influence on pain experience (López-Solà et al., 2019). This might explain why CT non-optimal touch was as effective in reducing pain experience as CT-optimal touch over the week.

Interestingly, it appears that CT-optimal touch does have an additional *immediate* pain relieving effect. This is in line with previous studies into acute pain and chronic pain in an experimental setting, in which CT-optimal touch was effective in reducing pain experience immediately (Di Lernia et al., 2020; Gursul et al., 2018; von Mohr, Krahé, et al., 2018). Compared to CT non-optimal touch, CT-optimal touch shows an additional pain relieving effect after 15 mi. Our results show that CT-optimal touch should at least be applied for 10 – 15 min to most effectively ameliorate pain. The optimal duration of CT-optimal touch is also in line with the study of Di Lernia et al. (2020) in which CT-optimal touch appeared effective after 11 min. This is consistent with the activation of the CT-fibers, as these are unmyelinated the processing is slower than that of the myelinated Aβ-fibers. Indeed, the conduction velocity of the Aβ-fibers is 60 m/s and that of the CT-fibers is 2 m/s (McGlone et al., 2014). Even though the conduction velocity of the CT-fibers is 30 times slower than that of the Aβ-fibers, the CT-fibers are still processed within seconds. We therefore speculate that the pain ameliorating effect of the CT-fibers needs time to build up and is most effective between 10 – 15 min. The difference in conduction velocity also further substantiates the involvement of Aβ-fibers in CT non-optimal touch as this was already effective between 0 – 5 min.

The effect of CT-optimal touch on chronic pain did not last the entire day. This shows that although CT-optimal touch has an additional immediate pain relieving effect on chronic pain compared to CT non-optimal touch, this effect appears to be of short duration. It might be that one week of CT-optimal touch administration is not long enough and that for a long-term diminishing effect touch should be applied for a longer period of time or more than twice a day. Alternatively, it might be that CT-optimal touch can only reduce pain immediately. In that case, it can be used when a patient is in need for immediate pain relief. However, one of the participants excluded from this sample did report a long-term significant pain relieving effect of CT-optimal touch which even persisted after touch application had stopped (Meijer et al., 2023). Therefore, it might be that certain individuals do experience additional benefits from CT-optimal touch and therefore further longitudinal research into the effect of CT-optimal touch on chronic pain experience is warranted.

Importantly, even though there is no difference between the effect of CT-optimal touch and CT non-optimal touch on pain experience over the week, CT-optimal touch is rated as significantly more pleasant. In addition, at least 10 participants and their partners subjectively reported at the end of the study, before debriefing, that they were planning on continuing CT-optimal touch administration as it felt most effective in diminishing their pain and it was more natural and pleasant to receive and apply. Participants who had higher pain levels during the evening also subjectively reported that it felt that CT-optimal touch effectively reduced this "worst pain" and this also improved their quality and ability to sleep through the night. So, even though a significant difference between CT-optimal touch and CT non-optimal touch is missing with respect to chronic pain reduction over the week, there appears to be a clear preference for CT-optimal touch by participants and their partners.

As CT-optimal touch is clearly perceived as more pleasant than CT non-optimal touch, a possible relation between the effects of CT-optimal touch on pain and perceived pleasantness is of interest. We therefore investigated whether there is a relation between the immediate effect of CT-optimal touch and its perceived pleasantness. Since no such relation was found, the immediate pain relieving effect of CT-optimal touch appears to be independent of its perceived pleasantness. A similar result has been reported before by Meijer et al. (2023); Meijer et al. (2021) and von Mohr, Krahé, et al. (2018). From the model of Meijer et al. (2022) it follows that CT-optimal touch may reduce pain from a bottom-up as well as a top-down process. The top-down process relies on downregulation of pain regions involved in the motivational aspects of pain processing, i.e. the Insula and ACC, regions which are also highly involved in the perceived pleasantness of CT-optimal touch (Gordon et al., 2013). As we did not find a relationship between perceived pleasantness and the pain relieving effect of CT-optimal touch, it seems that the pain relieving effect of CT-optimal touch might rely more on the bottom-up process. Here, the CT-fibers inhibit nociceptive input in the dorsal horn of the spinal cord, preventing pain signals from reaching sub(cortical) brain regions. However, as most patients were suffering from (lower) back pain and/or pain in the shoulders and neck, and touch was applied on the forearm, one could argue that this can not only be related to the bottom-up process as this occurs more peripheral. Therefore, as touch was mostly applied on a different body part from where the pain was experienced, top-down influences are likely involved . We speculate that this top-down process (i.e. downregulation through the Insula and ACC) might therefore rely on the activation of the CT-fibers instead of activation by the perceived pleasantness of touch. This would mean that the top-down influence is

not necessarily a pleasantness related regulatory system but relies on input from the CT-fibers. This notion is important as chronic pain can also affect how we perceive touch, e.g. neuropathic pain, and it has therefore been suggested that CT-optimal touch might be ineffective in this patient group (Nagi et al., 2011). However, the current results indicate that how CT-optimal touch is perceived, i.e. pleasant vs unpleasant, does not influence its pain ameliorating properties, a notion also emphasized by the single case report of Meijer et al. (2023) and the study of Di Lernia et al. (2020).

The current study has several strengths and limitations. A first strength is that this is the first longitudinal study into the effects of CT-optimal touch on chronic pain. Furthermore, this study shows that CT-optimal touch can be used in a home-setting and application can be done by a partner who received a short and simple training. During the study a total of 28 touch applications needed to be performed. Participants and partners reported they never missed a touch application throughout the study, even when 2 participants could not report their pain experience due to difficulties with Gorilla they did administer touch. We therefore believe that it is feasible to implement CT-optimal touch in daily life to reduce the chronic pain experience. The current study also has a number of limitations. One is that due to technical issues, resulting in problems with reporting chronic pain experience, the reliability of the data might be affected (possibly obscuring effects). Second, we have a relatively small sample size of n=18, which negatively influences the ability to generalize the results to a larger population. Finally, as this study is a within-subject design participants and their partners were not blinded. Even though the terms CT-optimal- or affective touch have not been used and the theoretical background was discussed with participants during the debriefing, it could be that during the study participants were aware of the differences in presumed effectiveness of the types of touch. However, we think it unlikely this would have influenced our results as we found no significant order effect. Based on our current study, we suggest that future studies employ a Randomized Control Design and administer touch for more than one week.

To conclude, the current study investigated whether CT-optimal touch can reduce chronic pain experience in PD patients. Overall, both CT-optimal and CT non-optimal touch are effective in relieving chronic pain compared to no touch, but there is an additional immediate relieving effect of CT-optimal touch compared to CT non-optimal touch. In addition, CT-optimal touch is perceived as more pleasant but this was not related to the pain reduction. We therefore speculate that CT-optimal touch might be used when there is a need for immediate pain relief. Furthermore, our current study shows that using

CT-optimal touch in a longitudinal design in which the partner applies touch is feasible, which further emphasizes the possibilities of using CT-optimal touch as a treatment for chronic pain.

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Author contributions

LLM: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Writing – original draft; Writing – review; Editing.
CR: Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review.
ZS: Data curation; Writing – original draft.
CD: Conceptualization; Funding acquisition; Methodology; Supervision; Writing – original draft; Writing – review.
MS: Conceptualization; Formal analysis; Funding acquisition; Methodology; Supervision; Writing – original draft; Writing – review.

Conflict of Interest

The authors have no conflict of interest to report.

Data availability statement

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Appendix

Table A1. Descriptive statistics

Variables	Mean (SD)	Possible range	N
Age	65.05 (11.38)	18 – 100	18
Gender: Male/Female	n.a.		 10/8
Type of pain: Musculoskeletal pain Radicular pain	n.a.		 10 8
Pain Intensity Score	5.94 (1.55)	0 – 10	18
KPDPS total score	37.05 (15.55)	0 – 168	18
QRI total score Participant Partner	 16.12 (1.91) 15.24 (1.83)	 6 – 24 6 – 24	 17^ 17^
QRI support score Participant Partner	 11.24 (.81) 10.29 (1.67)	 3 – 12 3 – 12	 17^ 17^
QRI conflict score Participant Partner	 4.88 (2.11) 4.94 (1.39)	 3 – 12 3 – 12	 17^ 17^

*n.a.= not applicable

^= data of one participant and partner is missing.

Table A2. Mean-difference and p-values for CT-optimal touch and CT non-optimal touch for the different timepoints

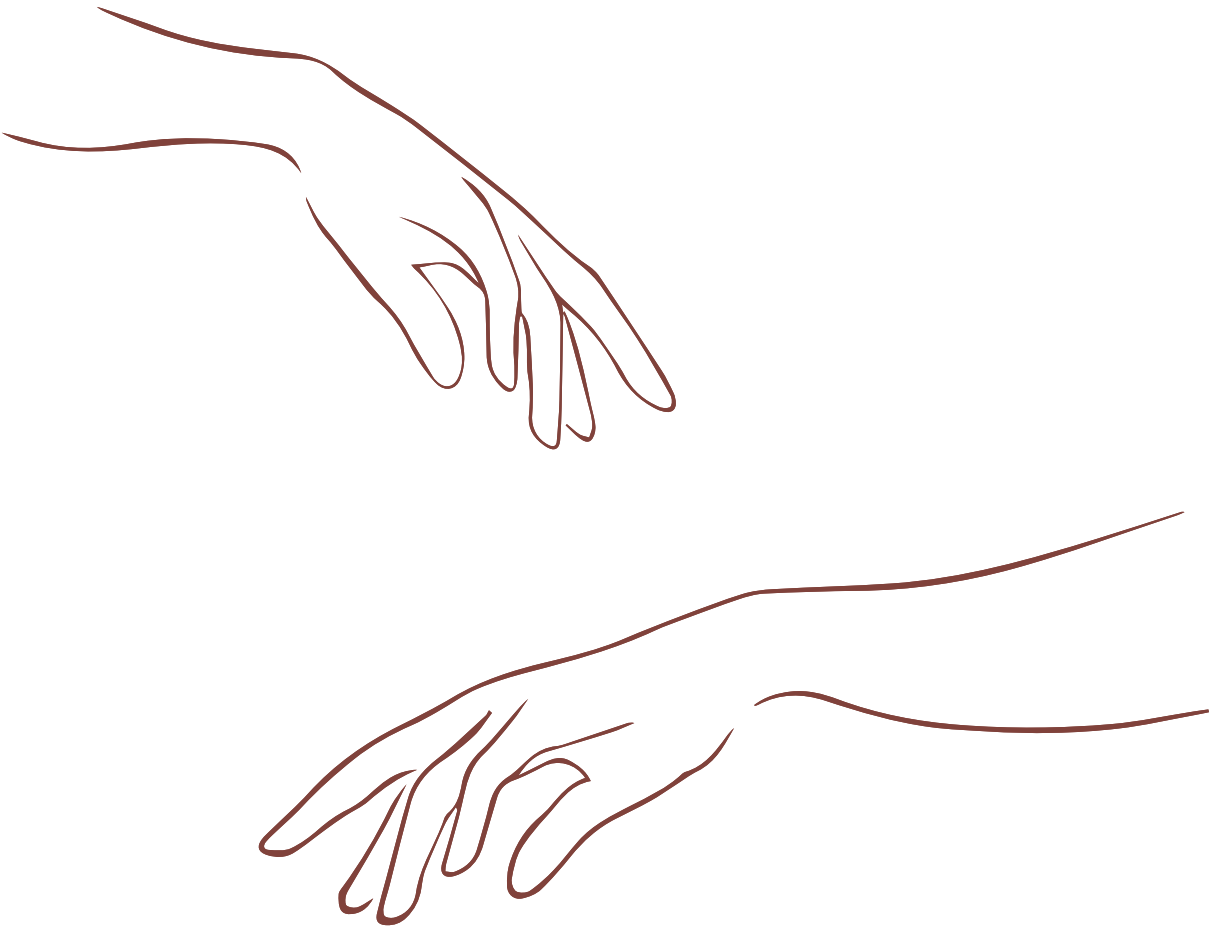
	CT-optimal touch		CT non-optimal touch	
	Mean difference	***p***	**Mean difference**	***p***
5 min – 0 min	-.30	.051	-.24	.004*
10 min – 0 min	-.59	<.001*	-.09	<.001*
15 min – 0 min	-.74	<.001*	-.48	.273
10 min – 5 min	-.29	.001*	-.21	.030*
15 min – 5 min	-.44	<.001*	-.25	.022*
15 min – 10 min	-.15	.081	-.03	1.00

*p<.05.

Outline of data processing

1) Data was retrieved from Gorilla, if needed Gorilla structure can be sent upon request.
2) Data was processed in Excel by creating different tabs for the no touch, CT-optimal touch and CT non-optimal touch condition.
3) In order to analyze data, averages of the FPS-R data for day 1 – day 7 were calculated. For the no touch week this means the average of the morning, afternoon and evening data points. For the CT-optimal touch and CT non-optimal touch condition this means the average of the morning and evening data when touch was administered en the afternoon data points when no touch was administered. Hereafter, data over the week was calculated by averaging day 1 – day 7.
4) FPS-R data was used to calculate difference scores to analyze the short-term effect. Difference scores were calculated by subtracting 0 min from 15 min, 5 min from 15 min and 10 min from 15 min. This was done for every day, whereafter data over the week was calculated by averaging day 1 – day 7. This was done for the CT-optimal touch condition and the CT non-optimal touch condition.
5) FPS-R data was used for the optimal touch duration analysis. In order to analyze this data, average for 0 min, 5 min, 10 min and 15 min were calculated. This was done for every day whereafter data over the week was calculated by averaging day 1 – day 7.
6) The VAS pleasantness means were calculated by averaging the VAS data points on 5 min, 10 min 15 min for morning and evening. This was done for every day whereafter data over the week was calculated by averaging day 1 – day 7.
7) For the PANAS scores a positive- and negative affect score was calculated. For the positive affect score, the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, 19 were added. For the negative affect score, the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, 20 were added. This was done for day 1 and day 7 and for CT-optimal touch and CT non-optimal touch condition.
8) All excel files were then imported to SPSS (version 28.0) to perform analyses.

Chapter 6



Spatial factors influencing the pain ameliorating effect of CT-optimal touch: A comparative study for modulating Temporal Summation of Second Pain

Larissa L. Meijer
Wouter Baars
H. Chris Dijkerman
Carla Ruis
Maarten J. van der Smagt

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Abstract

Recent studies show that CT-optimal touch can reduce pain. However, much is unknown regarding the factors influencing its pain ameliorating effect, such as tactile attention and touch application site. The current study investigates, in 36 healthy individuals, whether CT-optimal touch can reduce temporal summation of second pain (TSSP) compared to CT non-optimal touch and tapping the skin. All three conditions are applied on both the contralateral and ipsilateral side of pain induction. The results show that tapping the skin did not reduce TSSP, meaning that pain reduction through touch cannot be explained by tactile attention effects. CT non-optimal touch only reduced TSSP when applied on the ipsilateral side. Importantly, CT-optimal touch effectively reduced TSSP when applied on the contralateral and ipsilateral side. Furthermore, CT-optimal touch was more effective in reducing TSSP compared to CT non-optimal touch and Tapping when applied on the contralateral side. This effect was independent of perceived pleasantness. Interestingly, this difference between conditions was not present when CT-optimal touch was applied on the ipsilateral side. This study shows that that CT-optimal touch can reduce TSSP and this effect appears to be independent of touch application site, which is highly relevant for implementing CT-optimal touch as a treatment.

Keywords: CT-optimal touch, affective touch, Temporal Summation of Second Pain, chronic pain, tactile attention

6.1. Introduction

In 1990 a special subtype of unmyelinated low threshold mechanoreceptive C-fibers that respond to tactile input were discovered, and hence called C-tactile (CT) fibers (Nordin, 1990). These CT-fibers respond to gentle slow stroking of the skin at an optimal velocity of 3 cm/s with a range of 1 – 10 cm/s (Olausson et al., 2010). CT-optimal touch can elicit a pleasant sensation and is therefore also referred to as affective touch (Vallbo et al., 2009). Recent studies show that besides mediating tactile pleasantness, CT-optimal touch can reduce acute and chronic pain experience (Di Lernia et al., 2020; Fidanza et al., 2021; Gursul et al., 2018; Liljencrantz et al., 2017; Meijer et al., 2023; von Mohr, Krahé, et al., 2018). Based on these studies it appears that CT-optimal touch might be an interesting addition to current pain treatments. However, even though these studies show promising results, much is still unknown regarding the factors influencing the pain ameliorating properties of CT-optimal touch.

One of these factors is tactile attention. When touch is applied on the skin, our attention is almost automatically drawn towards that stimulus (Chapman, 2009). Previous studies show that attention can serve as a pain distractor (Bascour-Sandoval et al., 2019). However, these previous studies mostly used visual, auditory or cognitive tasks to distract from perceived pain. Whether tactile attention can also be used as a pain distractor therefore remains unknown. As the neurophysiological mechanisms underlying CT-optimal touch are not fully understood yet, it could also be that the previously found effects of CT-optimal touch on pain experience (partially) rely on attentional effects (von Mohr, Krahé, et al., 2018). Studies into the effect of CT-optimal touch on pain often use a faster touch as a control condition, also referred to as CT non-optimal touch. Even though CT-optimal touch is significantly more effective than CT non-optimal touch, CT non-optimal touch can also reduce pain experience to some extent (Gursul et al., 2018; Liljencrantz et al., 2017; Meijer et al., 2023; von Mohr, Krahé, et al., 2018). This might also be related to spatial tactile attention. Therefore, in the current study an extra stimulus condition (tapping instead of stroking) is used to control for this possible attentional effect.

Another factor influencing the pain ameliorating properties of CT-optimal touch might be touch application site. Most studies into the effect of CT-optimal touch on acute pain applied touch on the same body part as where pain was induced (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017). There are only two studies where touch application and nociceptive stimulation were spatially distinct (Krahé et al., 2016; von Mohr, Krahé, et al., 2018). In addition, there are two studies showing that CT-optimal touch effectively reduces chronic pain experience when applied on the same body part (Fidanza et al., 2021; Meijer et al., 2023). Another

study into CT-optimal touch and chronic pain experience did not report the exact body part affected by the chronic pain condition and it is therefore unclear whether touch application was, for instance, contralateral or ipsilateral to the pain location (Di Lernia et al., 2020). Taken together, current studies show that CT-optimal touch effectively reduces pain experience either ipsilateral or contralateral side to the pain location. However, none of these studies actually *compared* ipsilateral to contralateral touch application. Therefore, it is unknown if there is any difference in effectiveness. If we want to use CT-optimal touch as a chronic pain treatment, it is necessary to know whether its effect depends on touch application site. This is important as CT-fiber density is not evenly distributed across the body. Previous studies show that CT-fibers innervate the hairy skin and show high density on the face, forearm but to a lesser extent the leg (Watkins et al., 2021). Density of the CT-fibers in the whole human body has not been reported yet. However, studies into the density of animal CT-fibers suggest that density is higher in more proximal body parts (Ackerley, Carlsson, et al., 2014).

So, it seems that applying CT-optimal touch on the forearm or the face will most likely activate a high density of CT-fibers. Therefore, to reduce chronic pain it might be more effective to apply CT-optimal touch on a body part with a high CT-fiber density. However, the most common forms of chronic pain are osteoarthritis and (lower) back pain (Cohen et al., 2021), which are not the body parts containing the highest density of CT-fibers. As a proxy for same or different body part, this study investigates whether there is a difference in effectiveness between applying CT-optimal touch ipsilateral to nociceptive stimulation and contralateral to nociceptive stimulation. This will provide further information on the possibility to use CT-optimal touch as a generalized treatment for chronic pain (Meijer et al., 2022).

In order to study this we adapted a stimulation protocol from Fidanza et al. (2021) which uses repetitive heat pulses to induce Temporal Summation of Second Pain (TSSP) also referred to as wind-up pain. This paradigm activates C-nociceptors; by repetitively stimulating these fibers a burning and/or tingling sensation can be elicited (Staud et al., 2007). This is linked to central neuronal sensitization, a process related to chronic pain. Therefore, inducing TSSP in healthy individuals can serve as a model for chronic pain conditions (Staud et al., 2007). The study of Fidanza et al. (2021) shows that CT-optimal touch can reduce TSSP compared to a no touch condition and very slow (0.3 cm/s) touch. However, in this study CT-optimal touch was applied only ipsilaterally to nociceptive stimulation. Therefore, in the current study participants will undergo three types of tactile stimulation while TSSP is induced namely, CT-optimal touch (3 cm/s), CT non-optimal

touch (18 cm/s) and a Tapping condition. A velocity of 18 cm/s has proven to be an effective control condition for CT-optimal touch and is quite natural to apply (Meijer et al., 2023; Meijer et al., 2021; von Mohr, Krahé, et al., 2018). The Tapping condition is adapted from McIntyre et al. (2022) and will be used as a control condition for spatial tactile attention. All types of touch will be applied both ipsilaterally and contralaterally to nociceptive stimulation. We hypothesize that CT-optimal touch will effectively reduce TSSP compared to CT non-optimal touch and Tapping and that this effect will be larger when CT-optimal touch is applied on the ipsilateral side compared to the contralateral side (Meijer et al., 2023). Furthermore, similar to Fidanza et al. (2021) we also look into the relationship between body awareness and the pain-relieving effect of CT-optimal touch. Previous literature shows that the ability to detect internal states of the body i.e. body awareness, is related to pain perception (Cramer et al., 2018). Even more so, people suffering from chronic pain also report higher levels of body awareness (Kalkışım et al., 2022). Therapies targeting body awareness appear to reduce some forms of chronic pain (Matamala-Gomez et al., 2019). As such, we expect that participants with high body awareness report higher levels of pain and show a larger pain-diminishing effect.

6.2. Methods

6.2.1 Participants

A total of 38 healthy volunteers participated in this study between 01/06/2023 and 04/08/2023. The participants sample consisted of 20 males, 16 females and 2 participants whose gender was unspecified. The age range of the participants was between 18 and 32 (mean ± SD = 24.9 ± 3.3). Out of the 38 participants, 35 were right-handed. Any health conditions that could alter pain or tactile perception were considered as exclusion criteria. Two participants were excluded due to language barriers that hindered their understanding of the instructions. Prior to participation, all individuals provided written informed consent, and their identity was anonymized throughout the study. The study protocol (Protocol Number: 23-0147) was reviewed and approved by the local faculty ethical review board at the Faculty of Social and Behavioral Sciences, Utrecht University. This research adhered to the ethical principles outlined in the WMA Declaration of Helsinki 2013.

6.2.2 Thermal Stimulation

TSSP was induced using a TSA-II Neuro Sensory Analyzer (Medoc Ltd., Advanced Medical Systems, Ramat Yishai, Israel). A thermode (30 × 30 mm) was positioned on the ventral side of the participant's left wrist to deliver trains of 6 heat pulses at 0.33 Hz. The stimulation method, derived from Staud et al. (2007), involved continuous-contact heat application. Each pulse encompassed an ascending and descending temperature change of 8 °C/s, with a complete cycle lasting 3 s. Individual target temperatures were adjusted based on heat pain sensitivity, aiming for maximal thermal TSSP ratings of 45 ± 10 after 6 heat pulses at 0.33 Hz. Following each stimulus train, pain ratings were collected using a Computerized Visual Analogue Scale developed with the Gorilla Experiment Builder (www.gorilla.sc).

6.2.3 Tactile Stimulation

In the present study, participants underwent three distinct conditions of tactile stimulation simultaneously with the induction of temporal summation of second pain (TSSP). These tactile stimulation conditions were CT-optimal touch at a velocity of 3 cm/s, CT non-optimal touch at a velocity of 18 cm/s, and a Tapping condition. The order of tactile stimulation was perfectly counterbalanced between participants. All forms of tactile stimulation were applied both contralateral and ipsilateral to the nociceptive stimulation side, on the dorsal part of the participants' forearm. The CT-optimal and CT non-optimal touches were manually administered with a soft brush in a proximal-to-distal direction by a trained experimenter. The Tapping condition was administered as a continuous series of taps with random intervals of ~.1 to 2.5 s with a soft rubber tip of a pen, this method was adapted from McIntyre et al. (2022) and serves as a metric for evaluating spatial tactile attention.

6.2.4 Questionnaires

Pain perception was measured with a Visual Analog Scale (VAS) ranging from 0 – 100, in which 0 represented 'comfortable/unpainful' and 100 'uncomfortable/painful'. Similarly, the VAS for Pleasantness assessed tactile stimulus pleasantness on a scale from 0 'unpleasant' to 100 'pleasant'". To measure bodily awareness the Body Perception Questionnaire (BPQ-Short Form) was used (Cabrera et al., 2018). To rule out any possible order effects, half of the participants filled in the BPQ before the start of the experiment, while the other half filled in the BPQ at the end of the experiment.

6.3. Procedure

Upon arrival participants received and read the information letter. After addressing any questions arising from the information letter, participants provided written informed consent.

The participants were prevented from seeing the stimulated skin area using a curtain (see Figure 6.1). This was done to reduce visual distraction from the TSA device and to minimize a possible social component linked to touch administration.

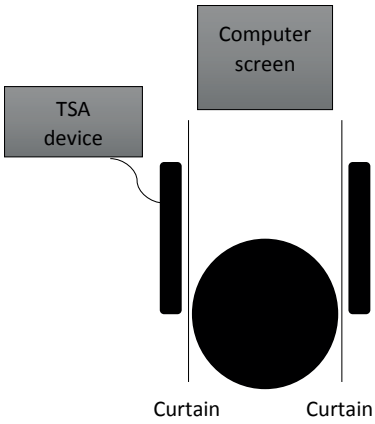

Figure 6.1. Schematic overview of experimental set-up

Before the experiment started, the experimenter marked an area of 18 cm on the dorsal side of the participants' forearms to ensure consistent manipulations. A preliminary demographic questionnaire containing age, gender and handedness was administered through a computer interface. In addition, the participant filled in the Body Perception Questionnaire (BPQ) either at the start of the experiment or at the end. After this, the correct temperature for the heat pulses was determined by starting at a temperature of 45° Celsius and increasing or temperature until participants reported 45 ± 10 on the VAS pain scale with a maximum temperature of 50.5° Celsius.

For a visualization of the study procedure see Figure 6.2. Before the start of every condition a baseline trial without any touch was conducted to establish a reference point for individual pain thresholds. Hereafter, touch was administered continuously over five trials in which TSSP was also conducted. Following each trial, participants filled in the VAS pain scale. Furthermore, participants rated the pleasantness of the touch at the conclusion of each condition. Intervals of 5 min were allocated as breaks after completing each

condition. Upon completion of the experiment participants were compensated in the form of course credits[1] or monetary remuneration. Any remaining queries were addressed before concluding the session.

6.4. Results

All data was processed using Microsoft Excel (version 2208) and analyzed with SPSS Statistics (version 28). Before the start of the experiment participants' baseline temperature was determined. Overall, the average baseline temperature was 49.01 °C (SD=1.72). The participants also filled out the Body Perception Questionnaire (BPQ) Short Form as a measure for body awareness. The participants average total item score was 38.08 (SD=10.12).

6.4.1 Main effect tactile stimulation

TSSP was measured with the VAS pain scale. Based on Fidanza et al. (2021) we calculated an average VAS pain score for every condition (T1-T5). As we used a baseline trial (a trial without touch) instead of a 'no touch' condition as used by Fidanza et al. (2021), a difference score for the VAS pain scale was calculated by subtracting the average of (T1-T5) from the baseline T0. This was done for all three types of tactile stimulation for both the contralateral and ipsilateral side (see Table 6.1).

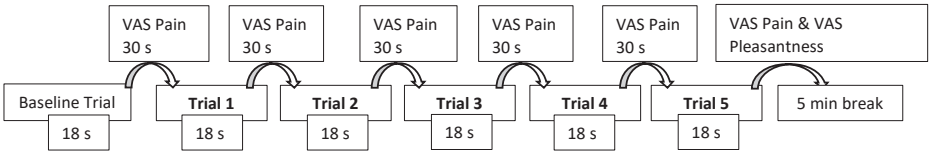

Figure 6.2. Schematic representation of a touch condition
During each condition 6 trials consisting of 6 heat pulses were delivered with a thermode on the ventral side of the participants left wrist. This thermode was calibrated before the start of the experiment per participant to elicit a tingling and burning sensation rated 45 ± 10 on the VAS pain scale. All three types of touch were administered continuously from trial 1 and onwards. One condition consists of one block on the contralateral arm and one on the ipsilateral arm.

1 As part of the Psychology Bachelor curriculum at Utrecht University students need to participate in research to obtain course credits.

Table 6.1. Mean difference scores on the VAS pain scale for every condition

	Mean difference score T0 – M(T1-T5)	STD
Tapping *contralateral*	4.93	13.08
Tapping *ipsilateral*	3.68	12.95
CT non-optimal touch *contralateral*	6.18	13.62
CT non-optimal touch *ipsilateral*	6.58	10.51
CT-optimal touch *contralateral*	12.54	13.23
CT-optimal touch *ipsilateral*	9.87	13.65

This data were checked for normality. Four out of six variables were not normally distributed according to the Shapiro – Wilk test. However, when visually inspecting the Q – Q plots and histograms, two of these four variables appeared normally distributed. To analyze the main effect for tactile stimulation type we decided to use a non-parametric test. A one sample Wilcoxon Signed Rank Test with test value 0, which would indicate a difference between T0 and M (T1-T5), and Bonferroni correction was used to analyze the data.

We found a significant effect for CT-optimal touch on both the contralateral and ipsilateral side. For CT non-optimal touch there was a significant effect on the ipsilateral side but not on the contralateral side. There was no significant effect for Tapping, meaning that tapping the skin did not significantly reduce pain experience (see Table 6.2).

Table 6.2. Results of one-sample Wilcoxon Signed Rank test with test value 0 for every condition

	T	p*
Tapping *contralateral*	2.20	.168
Tapping *ipsilateral*	2.41	.096
CT non-optimal touch *contralateral*	2.37	.108
CT non-optimal touch *ipsilateral*	3.55	<.006
CT-optimal touch *contralateral*	4.75	<.006
CT-optimal touch *ipsilateral*	3.78	<.006

* Two-sided Bonferroni corrected p-value

6.4.2 Difference between conditions

In order to investigate whether there was a significant difference between conditions, we decided to use a repeated measures ANOVA. Here, we also used the mean difference scores for the VAS pain scale. As only two out of six variables were not normally distributed, sample size was relatively large (N=36), a non-parametric alternative for a factorial ANOVA is not readily available, and it has been shown that Type 1 error and power of the F-statistic are not necessarily altered by violation of normality (Blanca et al., 2017), we decided that it was permitted to use a parametric test. Sphericity was violated so Greenhouse-Geisser corrections were used.

We found a significant main effect for condition $F(2,70)=6.28$, $p=.006$, partial $\eta 2= .15$ and observed power of .88. There was no significant main effect for stimulation site ($p=.421$), nor for the interaction condition*stimulation side ($p=.525$). Pairwise Bonferroni corrected comparison shows a significant difference between CT-optimal touch and Tapping ($p=.021$) and between CT-optimal touch and CT non-optimal touch ($p=.019$). There was no significant difference between CT non-optimal touch and Tapping ($p=.813$). When looking into the differences between conditions and taking stimulation side into account, there is a significant difference on the contralateral side for CT-optimal touch compared to CT non-optimal touch and Tapping (also see Table 6.3). Meaning that when CT-optimal touch is applied on the contralateral side it is more effective in reducing TSSP than CT non-optimal touch or Tapping the skin. This effect was not found for the ipsilateral side. The differences between conditions and touch sides for every trial are also depicted in Figure 6.3.

Table 6.3. Comparisons between conditions for the ipsilateral and contralateral side separately

Side	Conditions		p*
Contralateral side	CT-optimal touch	CT non-optimal touch	.02
		Tapping	.038
	CT-non optimal touch	Tapping	1.00
Ipsilateral side	CT-optimal touch	CT non-optimal touch	.348
		Tapping	.079
	CT-non optimal touch	Tapping	.722

*Bonferroni corrected p, with significance level at .05

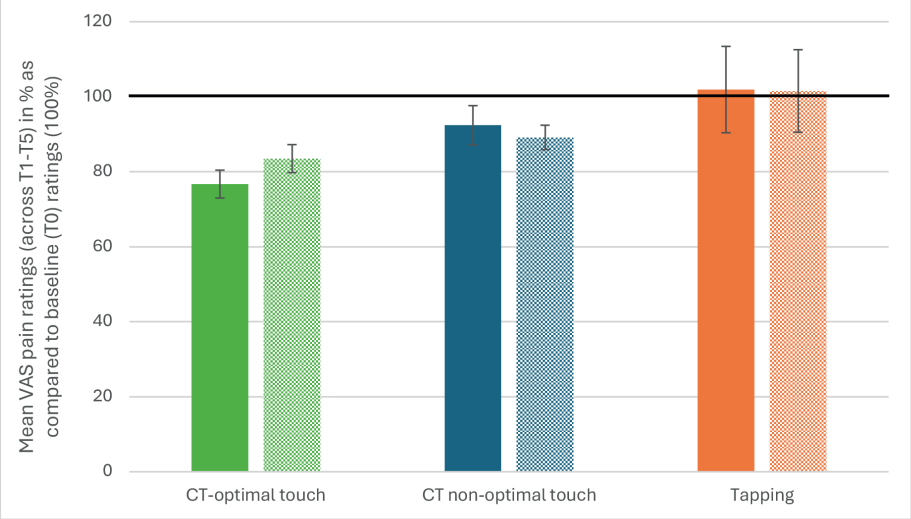

Figure 6.3. Mean VAS pain ratings (across T1-T5) in % as compared to baseline (T0) ratings (100%)
Filled bars depict contralateral administration, textured bars ipsilateral administration. Error bars depict ± 1 standard error of the mean.

We also looked into the difference between ipsilateral and contralateral touch application within touch conditions. Here we found no significant difference between contralateral and ipsilateral side for every condition.

6.4.3 Pleasantness tactile stimulation

The pleasantness of tactile stimulation measures with the VAS pleasantness was analyzed with a repeated measures ANOVA. Data was normally distributed; sphericity was violated so Greenhouse-Geisser corrections were used. One participant did not report pleasantness ratings for CT non-optimal touch, contralateral side therefore N=35. The VAS mean pleasantness ratings are depicted in Table 6.4.

Table 6.4. Mean and standard deviation (STD) of the VAS pleasantness for every condition

	Mean pleasantness	STD
Tapping *contralateral*	61.34	15.61
Tapping *ipsilateral*	57.89	16.94
CT non-optimal touch *contralateral*	69.63	19.03
CT non-optimal touch *ipsilateral*	71.37	16.30
CT-optimal touch *contralateral*	74.69	17.15
CT-optimal touch *ipsilateral*	70.77	15.86

The repeated measures ANOVA showed a significant main effect for condition $F(2,68)=10.37$, $p<.001$, partial $\eta^2=.23$ and observed power of .97. There was no significant difference for stimulation side (p=.263) and condition * stimulation side (p=.217). Pairwise Bonferroni corrected comparisons show a significant difference between CT-optimal touch and Tapping (p=.002) and between CT non-optimal touch and Tapping (p=.007). There was no significant difference between CT-optimal touch and CT non-optimal touch (p=1.00), meaning that both CT-optimal touch and CT non-optimal touch are perceived as more pleasant than Tapping.

When taking stimulation side into account similar effects were found. On the contralateral side there was a significant difference between CT-optimal touch and Tapping (p=.002) but not between CT non-optimal touch and Tapping (p=.108) and not between CT-optimal touch and CT non-optimal touch (p=.343). For the ipsilateral side we also found a significant difference between CT-optimal touch and Tapping (p=.012) and between CT non-optimal touch and Tapping (p=.006), but not between CT-optimal touch and CT non-optimal touch (p=1.00). Meaning that CT-optimal touch and CT non-optimal touch were perceived as more pleasant than Tapping, but there was no difference in perceived pleasantness between CT-optimal touch and CT non-optimal touch.

There were no significant differences within touch conditions between the ipsilateral and contralateral side.

6.4.4 Other analyses

To determine if there is any relationship between the pain ratings and perceived pleasantness of CT-optimal touch a Spearman correlation was used. This shows that there is no significant correlation between CT-optimal touch and perceived pleasantness on the contralateral side ($\rho= .29$, p=.082). However, there was a significant effect between CT-optimal touch and perceived pleasantness on the ipsilateral side ($\rho= .42$, p=.010).

In addition, we also analyzed whether there was a correlation between the pain ratings and the BPQ scores. Spearman correlations showed no significant correlation between the BPQ scores and CT-optimal touch on either the contralateral side ($\rho= -.03$, p=.845) or the ipsilateral side ($\rho= .12$, p=.493). There was also no significant correlation between the BPQ scores and baseline temperature and related pain rating ($\rho= -.13$, p=.456).

Furthermore, we analyzed whether there was a correlation between baseline temperature determined at the start of the experiment and the pain ratings. Again, Spearman correlations showed neither a significant correlation between baseline temperature and related pain rating for CT-optimal touch on

the contralateral side (ρ= .14, p=.404) nor for CT-optimal touch on the ipsilateral side (ρ= .15, p=.376).

As CT non-optimal touch on the ipsilateral side also significantly reduced pain, we also investigated whether there this ipsilateral effect was related to pleasantness, the BPQ scores and baseline temperature. Spearman correlations showed neither a significant correlation between CT non-optimal touch (on the ipsilateral) side and pleasantness (ρ= .22, p=.207), nor the BPQ scores (ρ= .27, p=.112). A lack of correlation was also apparent between baseline temperature and related pain rating (ρ= .04, p=.802).

6.5. Discussion

Previous research has shown that CT-optimal touch can reduce pain in healthy individuals (Gursul et al., 2018; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018) and in chronic pain patients (Di Lernia et al., 2020; Meijer et al., 2023). In addition, the study of Fidanza et al. (2021) shows that CT-optimal touch can also reduce Temporal Summation of Second Pain (TSSP). This is interesting as it appears that TSSP induced in health individuals can serve as a model for chronic pain (Staud et al., 2007). However, in this study touch was only applied on the same body part as where TSSP was induced. As CT-optimal touch appears to reduce chronic pain as well, it is necessary to investigate which factors contribute to this effect. Two of these factors might be spatial tactile attention and touch application site. As touch in general can also generate attention to the stimulus touching the skin, it could be that previously found effects of CT-optimal touch on pain rely mainly on attentional effects (Bascour-Sandoval et al., 2019; von Mohr, Krahé, et al., 2018). Therefore, in this study we investigated whether spatial tactile attention could influence the pain experience. Furthermore, touch was applied on both the ipsilateral and contralateral side of TSSP induction.

In the current study we show that CT-optimal touch when applied either on the contralateral or ipsilateral side effectively reduces TSSP. For CT non-optimal touch this effect was only found for the ipsilateral side. These effects were independent of participants' baseline temperature and related pain rating. Furthermore, we show that tapping the skin, used as a form of directing tactile spatial attention, does not reduce TSSP. Therefore, the pain ameliorating effect of CT-optimal and CT non-optimal touch cannot be explained by tactile attention, i.e. using touch as a distractor is not sufficient to reduce experienced pain. This is not in line with previous studies into the effect of attention on pain (Bascour-Sandoval et al., 2019). However, previous studies mostly used visual, auditory

or cognitive tasks as a distractor. There are only a few studies in which a tactile condition was used as a pain distractor, most of which used a very different type of tactile distraction i.e. non-painful electrical stimulation (Bascour-Sandoval et al., 2019). One study used tactile vibration as a tactile distractor, which seems more in line with the tactile Tapping condition used in the current study (Van Ryckeghem et al., 2013). Here, they found that tactile vibration did not significantly reduce pain experience, which is in line with our results.

Furthermore, we also looked at the difference in pain reduction between conditions. Here, we show that there is a significant difference between CT-optimal touch, CT non-optimal touch and Tapping. When we take stimulation site into account, CT-optimal touch is more effective in reducing TSSP compared to CT non-optimal touch and Tapping when applied on the contralateral side. This is in line with the studies of von Mohr, Krahé, et al. (2018) and Krahé et al. (2016), which also showed that CT-optimal touch can reduce acute pain when applied contralateral to the nociceptive stimulus. Surprisingly, this difference between conditions diminishes when CT-optimal touch is applied on the ipsilateral side. This is not in line with the study of Fidanza et al. (2021) as they do show a difference between CT-optimal touch, no touch and slower touch when applied on the same body part. In addition, a very recent study of Meijer et al. (2023) showed that CT-optimal touch effectively diminished chronic pain compared to CT non-optimal touch when applied on the same body part. However, the above-mentioned studies only applied touch either ipsilaterally or contralaterally to perceived pain location which makes it difficult to directly compare these studies with ours. Even though we did not find a significant difference between conditions when touch is applied on the ipsilateral side, we do show that CT-optimal touch also effectively reduced pain when applied on the ipsilateral side. Interestingly, there is no significant difference between the effectiveness of CT-optimal touch when applied on the contralateral or ipsilateral side.

Taken together, this shows that CT-optimal touch can reduce TSSP compared to CT non-optimal touch and Tapping. Specifically, it appears that this effect is independent of touch application site. Meaning that applying CT-optimal touch on the pain location is as effective as applying touch on a different bodily location. This indicates that it might be more effective to choose a bodily location that contains a high CT-fiber density than applying CT-optimal touch on the precise pain location. However, while CT-optimal touch shows similar effects on TSSP for application on both the contralateral and ipsilateral sides, compared to the other touch conditions, the effect of CT-optimal touch on TSSP appears larger when applied on the contralateral side. We therefore speculate,

that when touch is provided ipsilaterally, the peripheral system can inhibit the C-nociceptors at the level of the spinal cord and thereby preventing further pain processing. However, this system may not be as strong as the higher-order top-down regulatory system in the insula (Meijer et al., 2022). When touch is applied ipsilaterally the peripheral system is activated first, CT-optimal touch already interferes with pain processing on the level of the spinal cord and top-down regulation might not be activated. When touch is applied contralateral the top-down regulatory system is directly activated and this might result in a larger pain relieving effect (Meijer et al., 2022). Interestingly, TSSP or wind-up pain is not a peripheral tissue effect but depends more on central and descending pain processing pathways (Staud, 2013). It could therefore be that it is more effective to reduce TSSP through the CT-optimal touch top-down regulatory system instead of inhibition at a peripheral level, which might explain why we did find a difference between conditions when touch is applied on the contralateral side but not for the ipsilateral side.

Importantly, after the study some participants subjectively reported that when touch was applied on the ipsilateral side it sometimes appeared to synchronize with the TSSP induction. This caused a feeling of sensory overload due to which CT-optimal touch seemed to be overruled by the TSSP induction resulting in higher pain ratings compared to the contralateral side. This is important as this might influence the effectiveness of CT-optimal touch. However, if CT-optimal touch will eventually be used as a treatment for chronic pain this effect might not be present. As chronic pain is a constant internal bodily state instead of external pain induction with a device, the observed synchronization in the present study might be unlikely. This is substantiated by the study of Meijer et al. (2023) in which a patient suffering from chronic pain reported complete pain amelioration after ipsilateral CT-optimal touch. It is therefore important to further investigate the difference in CT-optimal touch application sites in an experimental setting as well as in chronic pain patients.

We also looked at the perceived pleasantness of the touch conditions. We show that Tapping is perceived as less pleasant compared to CT-optimal touch and CT non-optimal touch. There was no difference between CT-optimal touch and CT non-optimal touch. This is not in line with previous research showing that CT-optimal touch is perceived as more pleasant than CT non-optimal touch (Fidanza et al., 2021; von Mohr, Krahé, et al., 2018). However, in the study of von Mohr, Krahé, et al. (2018) pleasantness ratings were collected prior to pain stimulation. In our study and that of Fidanza et al. (2021) pleasantness was reported at the end of each block. In contrast, the study of Fidanza et al. (2021) used a very slow touch as CT non-optimal touch instead

of a velocity of 18 cm/s used in the current study. Therefore, it is difficult to directly compare these results. Interestingly, a very recent study shows that the affective and pleasant perception of touch also rely on the Aβ-fibers (Schirmer et al., 2023). As such, touch can also be perceived as pleasant and affective without activating the CT-system. This could explain why we did not find a difference in perceived pleasantness between CT-optimal touch and CT non-optimal touch.

Moreover, there was in general no relationship between perceived pleasantness and the pain-relieving effect. It is therefore unlikely that the pain-relieving effect depends on perceived pleasantness and related top-down analgesic effects (Elias & Abdus-Saboor, 2022). The pain-relieving effect of CT-optimal touch appears to be related to activation of the CT-system and the underlying pain-diminishing mechanisms (Meijer et al., 2022).

As mentioned, CT non-optimal touch only effectively reduced pain when applied on the ipsilateral side. This might be explained by the Gate Control Theory (Melzack & Wall, 1965), which refers to a 'gate' in the spinal cord which can be closed to interfere with pain processing. Closing the 'gate' appears to be related to activation of the large myelinated Aβ-fibers. The Aβ-fibers can be activated by stroking or rubbing the painful body part at a relatively high velocity (McGlone et al., 2014). The Gate Control Theory therefore appears to be based on a peripheral mechanism which can only be activated when touch is applied on the painful body part. As we used a velocity of 18 cm/s for the CT non-optimal touch condition is it likely that the Aβ-fibers were activated and thereby the 'gate' to interfere with pain processing. This is further substantiated by the observation that CT non-optimal touch applied on the contralateral side was ineffective and that there was no relationship with perceived pleasantness. The effect of CT non-optimal touch is likely related to the peripheral Gate Control Theory instead of more top-down related processes such as pleasantness related analgesia (Elias & Abdus-Saboor, 2022).

In our study we also looked into the possible relationship between body awareness and pain. We expected that participants who report high levels of body awareness are also more sensitive to pain and would show a larger pain-diminishing effect (Cramer et al., 2018; Kalkışım et al., 2022; Matamala-Gomez et al., 2019). However, we did neither find a relationship between body awareness and pain perception nor for the pain-relieving effect either for CT-optimal touch or CT non-optimal touch applied on the ipsilateral side. This shows that in this study body awareness did not influence pain perception or the pain-relieving effect of touch.

One major limitation of the current study was that we did not counterbalance between contralateral and ipsilateral touch application. During the set-up of this study our goal was to counterbalance every condition, however we believed that full counterbalancing could potentially lead to an increased transfer of effects between conditions. The interaction between stimuli might result in unintended influence bleeding over from one condition to another, possibly obscuring the effects we aimed to study. Therefore, we decided to only counterbalance the touch conditions perfectly, but fix the stimulation side order. Based on current knowledge of the CT-system and the two mechanisms involved in its pain relieving effect (Meijer et al., 2022), we hypothesized that starting on the ipsilateral side would increase the chance of unintended bleeding over effects. This because when CT-optimal touch is applied on the ipsilateral side it is likely that both the peripheral and top-down pain inhibiting mechanisms are activated. Therefore, we believed that starting on the contralateral side would decrease the chance of activating the peripheral inhibitory system and thereby only activating the top-down regulatory mechanism. However, even though we did counterbalance between conditions it is recommended to study the effect of CT-optimal touch on both contralateral and ipsilateral side while counterbalancing these conditions as well. In addition, it is interesting to add neurophysiological measures such as EEG to measure the amplitude of the N1, N2 and P2 complexes as these are related to noxious processing and compare this when CT-optimal touch is applied on the ipsilateral and contralateral side (von Mohr, Krahé, et al., 2018).

To conclude, we show that CT-optimal touch can reduce pain compared to CT non-optimal touch and Tapping. Furthermore, this study shows that spatial tactile attention is ineffective in reducing temporal summation of second pain. Therefore, tactile attention cannot explain the effect of touch on pain perception. Interestingly, the pain-ameliorating effect of CT-optimal touch appears independent of touch application site. Therefore, it seems that CT-optimal touch can also be applied on a different bodily location than on the pain location itself, which is highly relevant for implementing CT-optimal touch as a treatment.

Author contributions

L.L.M: Conceptualization; formal analysis; methodology; visualization; writing –original draft. **W.B.:** Conceptualization; data curation; methodology; visualization; writing –original draft. **H.C.D:** Conceptualization; methodology; supervision; writing –original draft. **C.R.:** Conceptualization; supervision; writing –original draft. **M.J. van der S.:** Conceptualization; formal analysis; methodology; supervision; writing –original draft.

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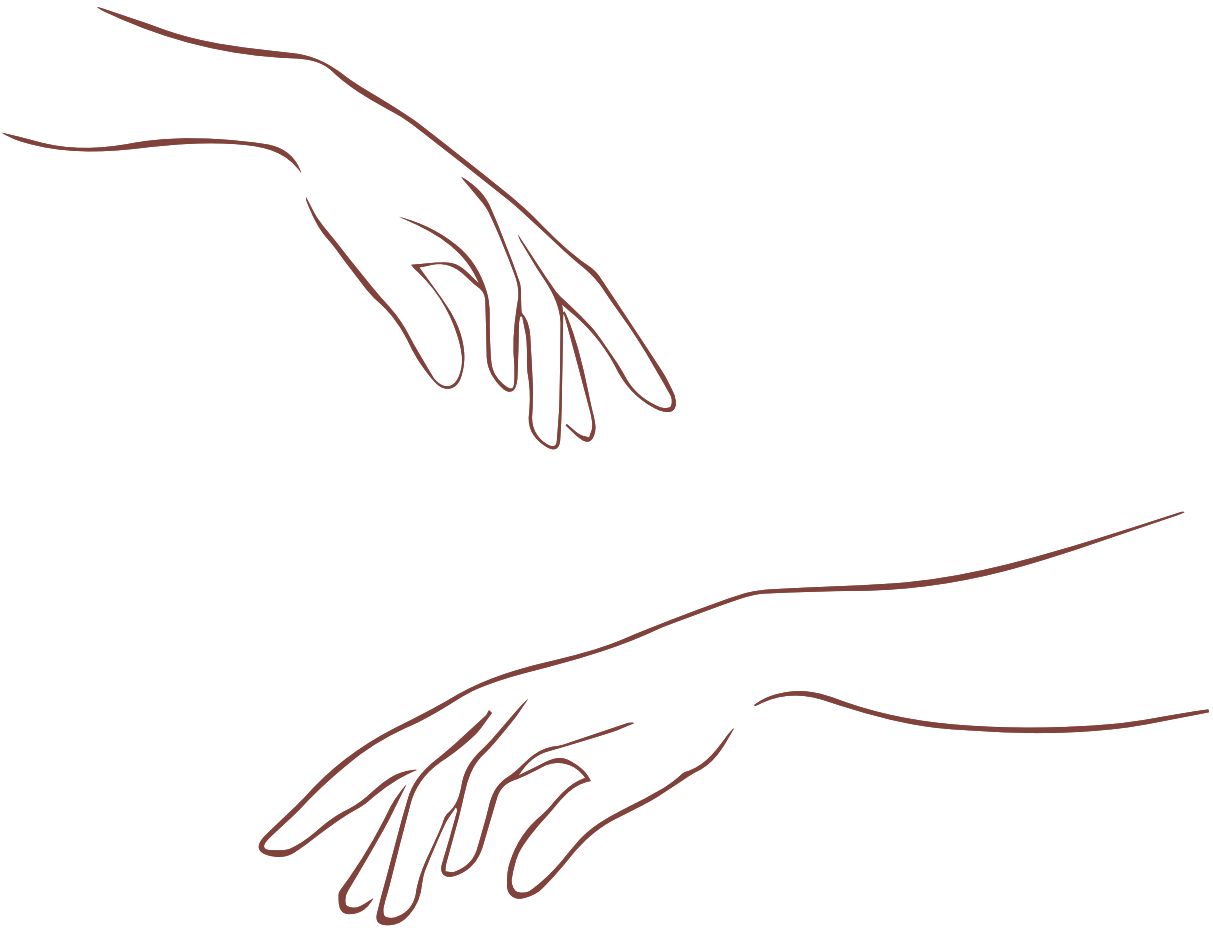
Conflict of Interest

The authors have no conflict of interest to report.

Data availability statement

The anonymous data supporting the findings of this study will be made publicly available after publication through the data management service YODA, a data sharing tool from Utrecht University.

Chapter 7



Affective touch perception and longing for touch during the COVID-19 pandemic

Larissa L. Meijer
B. Hasenack
J. C. C. Kamps
A. Mahon
G. Titone
H. C. Dijkerman
A. Keizer

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Abstract

Interpersonal touch and affective touch play a crucial role in social interactions and have a positive influence on mental health. The social distancing regulations implemented during the COVID-19 pandemic have reduced the ability to engage in interpersonal touch. This could cause longing for touch, and it might subsequently alter the way in which affective touch is perceived. To investigate this, we conducted an online survey and included 1982 participants, which contained questions regarding the COVID-19 regulations, longing for touch, and the perceived pleasantness of affective and non-affective touch. Results showed that participants reported feelings of longing for touch. This significantly increased with the duration and severity of the COVID-19 regulations. In addition, participants who experienced more longing for touch rated videos of affective and non-affective touch as more pleasant. Current results provide insight in the impact of sudden and prolonged COVID-19 regulations and show that increasing the duration and severity of these regulations is associated with a higher desire for touch, which is associated with increased perceived pleasantness of observing touch.

7.1. Introduction

To contain the outbreak of the COVID-19 virus, a variety of public health measures have been implemented globally to limit physical and social interactions. One aspect of social interactions that has been particularly affected by these public health measures is the ability to engage in social touch (Verity et al., 2020). Regulations such as quarantine and social distancing minimize social touch interactions with people outside the own household. Recently, first evidence emerged showing that the restrictions to contain the COVID-19 pandemic are linked to self-reported touch deprivation (Field et al., 2020; Von Mohr et al., 2021). Longing for touch during the COVID-19 pandemic potentially has a large impact on our well-being and social life, as research shows that touch plays an integral role in social interactions (Morrison et al., 2010). It promotes the formation and maintenance of social bonds (Dunbar, 2010), helps to convey emotions (Hertenstein et al., 2006), facilitates prosocial behavior (Morrison et al., 2010) and reduces feelings of ostracism (von Mohr et al., 2017). Moreover, research shows that interpersonal touch is important for social support and has a positive impact on mental health. For example, holding hands with a loved one can reduce anxiety and pain (Coan et al., 2006; López-Solà et al., 2019) and massages have a positive effect on psychological symptomatology (T. Field, 2019). In addition, interpersonal touch is associated with a higher quality of life (Floyd, 2014). Indeed, pre-COVID-19 research showed that touch deprivation increases stress, disrupts psychological resilience as well as coping with stressful situations, which can increase the risk of developing anxiety disorders and depression (Banerjee et al., 2021). However, these previous studies have not been performed during global social distancing measures but focused on individuals who experienced touch deprivation even under unrestricted societal circumstances (Field, 2010). As such these previous findings have a limited generalizability, as during the COVID-19 pandemic a vast majority of the adult general population experienced a reduction in touch frequency, regardless of, for example, their mental health status, age or gender. It is therefore crucial to examine longing for touch in the general population during the COVID-19 pandemic, as this will further our understanding of the impact social distancing has on individuals.

Affective touch is a form of interpersonal touch that has been suggested to have beneficial effects for the individual that is being touched (Björnsdotter et al., 2010). Affective touch refers to a gentle and slow (1 – 10 cm/s) stroking of the skin that is generally experienced to be very pleasant (McGlone et al., 2014). Gentle stroking at 1 – 10 cm/s (optimally at 3 cm/s) activates specific unmyelinated low-threshold mechanosensory C-fibers namely, C-tactile (CT) afferents, therefore it is also referred to as CT-optimal touch. CT-afferents are mostly located in the

hairy skin (Vallbo et al., 1999), but also see (Watkins et al., 2021). The CT-system contains a distinct neural pathway projecting to cortical areas mostly involved in affective and emotional processing, i.e. the insula and anterior cingulate cortex (ACC) (Löken et al., 2009). These areas have been suggested to account for the affective component of this kind of touch (Banerjee et al., 2021). Besides bottom-up processing of CT-optimal touch, top-down processes, such as contextual and social factors (e.g. the intentions of the toucher, the relationship between the toucher and the individual being touched) play an important role in the appraisal of CT-optimal touch as well (Banerjee et al., 2021; McGlone et al., 2014). Even more so, several studies show that the top-down processes involved in CT-optimal touch are related to its beneficial effects. Several studies show that when someone is touched by their romantic partner they experience stronger pain reduction compared to being touched by an experimenter (Krahé et al., 2016; Krahé et al., 2018).

In addition to contextual and social factors, other factors such as age (Sehlstedt et al., 2016), presence of psychological disorder (Croy et al., 2016) and exposure to touch (Sailer & Ackerley, 2019) play a top-down role in individual differences in CT-optimal touch perception. Sailer and Ackerley (2019) found that adults who reported infrequent interpersonal touch experiences perceived CT-optimal touch to be less pleasant than those who reported a higher interpersonal touch frequency. Sailer and Ackerley (2019) postulate that infrequent interpersonal touch results in a decrease in CT-optimal touch processing. As such, touch frequency appears to impact the appraisal of CT-optimal touch. This is especially of interest during the COVID-19 pandemic, as social distancing regulations might influence the amount of touch individuals receive. Changes in touch frequency as a result of COVID-19 might be associated with how CT-optimal touch is appraised and the extent to which individuals can benefit from the positive (mental health) effects of CT-optimal touch.

The first aim of the current study was to examine the link between the duration and severity of COVID-19 regulations and self-reported longing for touch in an adult community sample, while also taking certain socio-demographic factors into account, such as age (Sehlstedt et al., 2016), gender (Croy et al., 2014) and living conditions (e.g. living with a romantic partner or alone). We expected participants' level of longing for touch to increase with the duration of social distancing regulations. This is in line with very recent work by Von Mohr et al. (2021) who showed that during the COVID-19 pandemic individuals crave social touch and that this craving increases with the duration of social distancing measures.

The second aim of the current study was to explore the relation between longing for touch and perceived pleasantness of touch. The perception of CT-optimal and CT non-optimal touch is typically studied using an in-person paradigm in which participants are touched by the experimenter. Due to the COVID-19 pandemic it was not possible to physically interact with participants at the time of testing. We therefore included a touch paradigm in which participants observed and evaluated videos of CT-optimal and CT non-optimal touch (Lee Masson et al., 2018; Willemse et al., 2016). Previous research shows that the mere observation of CT-optimal touch activates similar brain areas, e.g. the insula, as during the actual physical experience of CT-optimal touch (Lee Masson et al., 2018). Furthermore, the perceived pleasantness of observed touch also interacts with the stroking velocity (Willemse et al., 2016). Specifically, and similar to results from in person studies, participants tend to rate the observation of CT-optimal touch as more pleasant than the observation of CT non-optimal touch. Therefore, touch observation seems a reliable way to assess perception of CT-optimal and CT non-optimal touch in the current study. In addition, several factors that might influence the perception of touch were taken into account, including for example age (Sehlstedt et al., 2016) and gender (Croy et al., 2014). Following Sailer and Ackerley (2019) we expected that an increase in longing for touch would be related to a decrease in pleasantness ratings of CT- optimal touch videos.

7.2. Methods

7.2.1 Participants

Between April 5th and October 8th 2020, 2403 participants completed the experiment in Qualtrics. In the analyses we only included participants older than 16, who had not been diagnosed with a mental, neurological, or skin disorder and who reported that COVID-19 public health regulations were currently in effect in their country of residence. This resulted in excluding 373 participants. In addition, another 48 participants with anomalous scores on the duration of regulations variable (+ 3 SD) were excluded. This resulted in a final dataset for analyses consisting of 1982 participants. The majority of these participants were female (n= 1579) and aged between 16 and 87 (M = 38.53, SD = 15.62). All participants provided written informed consent at the start of the experiment and did not receive any form of compensation. The study was approved by the local faculty ethical review board of Utrecht University (protocol number 20-210) This study was conducted in line with the WMA Declaration of Helsinki (Fortaleza, Brazil, 2013).

Most participants lived in the Netherlands (68.1%) or Italy (11.2%) and were experiencing a lockdown at the time of testing (68.1%). This means that the government advised them to stay at home as much as possible and that social gatherings and social interactions were prohibited. Participants estimated that the COVID-19 regulations in their country of residence had been in place for an average of 42.81 days at the time of testing (SD = 23.92; 0 – 130). The majority of participants were not and had not been infected with the COVID-19 virus at the time of the experiment (75.4%), 22.7% was not sure if they had been infected. In addition, most participants were working or studying from home (59.7%) and were living with housemates with whom they had a good relation- ship (61.1%). A complete overview of the demographic characteristics of the sample can be found in the Table 7.1.

7.2.2 Materials

Perceived pleasantness of touch videos. Participants watched two videos that depicted a forearm being stroked with a hand at a CT-optimal (3 cm/s) and CT non-optimal (30 cm/s) velocity. Each video had a duration of 10 s and the order of the videos was counterbalanced across participants (see Supplementary Materials S1 for videos). The participants completed a touch perception questionnaire after watching each video. Participants responded to five statements regarding the pleasantness of the touch: "1. How did the videoclip make you feel? 2. How do you think the person giving the touch would rate the touch? 3. How do you think the person being touched would rate the touch? 4. How would you rate the touch? 5. How much would you like to be touched like that?" Responses were given on a 10-point scale ranging from 0 ("Very unpleasant") to 10 ("Very pleasant"). A mean score was subsequently calculated, with a higher score indicating that the touch observed in the video was perceived as pleasant. Cronbach's α was 0.918 for CT non-optimal velocity and 0.919 for CT-optimal velocity, demonstrating high reliability.

7.2.2.1 Demographic information

Information about sample characteristics (age, gender and the presence of mental/neurological disorders, current work situation) and the current COVID-related regulations (duration and severity) was obtained at the start of the study (see Supplementary Materials S1 for all demographic questions). Participants also answered a number of questions about their living conditions, including if they lived with housemates and/or pets and how they would rate the quality of their relationship with potential housemates. The latter was rated on a 10-point scale ranging from 1 ("Very Poor") to 10 ("Very Good"). We categorized living

conditions into: living without housemates and pets, living with pets, living with housemates with whom relationship quality was poor (Quality relationship< 5), and living with housemates with whom relationship quality was good (Quality relationship> 5).

7.2.2.2 Longing for touch

A 2-item questionnaire was used to measure longing for touch ("Currently I would prefer to be touched by others ..." and "Currently I would prefer to touch others ..."). Participants responded using a scale that ranged from 0 ("Currently I would prefer to be touched less by others/to touch others less") to 10 ("Currently I would prefer to be touched more by others/to touch others more"). To calculate an average longing for touch score, the mean response was taken across these two items. Higher average scores (> 5) indicated that participants felt touch deprived. There was a high reliability between these items (Cronbach's α= 0.922).

7.2.3 Data analyses

SPSS 24.0 was used to analyze the data. Data were checked for normality with a Shapiro – Wilk test and a Q – Q plot. The plots were used as additional check because of the sensitivity of the Shapiro – Wilk test to large sample sizes (Ghasemi and Zahediasl 2012). Scores on the longing for touch questionnaire were not normally distributed, as indicated by both the Shapiro – Wilk test ($p < 0.05$) and the Q – Q plots. A multiple linear regression with bootstrapping (1000 iterations) was therefore used to analyze these data. The Shapiro – Wilk test also indicated that the responses to the touch perception questionnaire were not normally distributed ($p < 0.05$). However, Q – Q plots demonstrated that these scores were approximately normally distributed. Therefore, regular linear regressions were used to analyze these variables. For all tests, the other assumptions were met. For all regressions, the VIF values for the continues variables were below 5, indicating that multicollinearity did not affect the results. Since we were dealing with a large data set we set $\alpha = 0.01$ (two-tailed), unless stated otherwise.

Table 7.1. Demographics of sample population

Variables	n	%
Gender		
Male	396	20.0
Female	1579	79.7
Non-binary	7	0.4
Location		
Europe	1816	91.6
North America	33	1.7
Australia + New Zealand	9	0.5
Asia	7	0.4
South America	4	0.2
Africa	2	0.1
Severity of regulations		
Advice to not shake hands	34	1.7
Advice not to engage in social interactions (social distancing)	402	20.3
Lockdown	1232	62.2
Complete lockdown	314	15.8
COVID-19		
I am currently infected	5	0.3
I was infected in the past	29	1.5
I am/have not been infected	1494	75.4
I am unsure	449	22.7
Living conditions		
Living alone without housemates/pets	429	21.6
Living without housemates, but with pets	135	6.8
Living with housemates, poor relationship	129	6.5
Living with housemates, good relationship	1211	61.1
Current employment status		
Unemployed	302	15.2
Working or studying from home	1183	59.7
Working or studying at an external location	312	15.7
At home but unable to work/study	181	9.1

7.3. Results

7.3.1 Longing for touch

A score of 5 on the longing for touch questionnaire would reflect a perfect balance between touch wish and touch frequency. In the current sample 82.9% (n= 1644) of the participants scored higher than 5. The average score on the longing for touch questionnaire was 7.70 (SD = 2.31). A one sample t-test with a test value of 5 showed that participants scored significantly higher than 5, $t(1881)= 50.85$, $p < 0.001$, Cohen's $d= 1.17$, suggesting that participants reported to experience a longing for touch.

A multiple linear regression with bootstrapping was used to investigate the influence of the duration and severity of COVID-related regulations and four socio-demographic factors (age, gender, living conditions, cur- rent work situation) on longing for touch. The overall regression model was significant, $F(13, 1796) = 14.96.24$, $p < 0.001$, $R2 = 0.10$. The regression coefficients are displayed in Table 7.2.

Table 7.2. Regression coefficients with longing for touch as outcome measure

Model	B	Std. error	β	*p*
(Constant)	5.99 (5.42, 6.48)	0.28	–	0.001
Duration of regulations	0.02 (0.01, 0.02)	0.00	0.17	0.001
Regulation severity				
ANSH vs. complete lockdown	−0.15 (−1.09, 0.78)	0.44	−0.01	0.713
Social distancing vs. complete LOCKDOWN	0.33 (−0.61, 0.77)	0.20	0.06	0.101
Lockdown vs. complete lockdown	0.30 (−0.01, 0.65)	0.17	0.06	0.080
Age	0.00 (−0.01, 0.01)	0.00	0.02	0.600
Gender				
Non-binary vs. men	1.47 (0.46, 2.52)	0.54	0.04	0.002
Women vs. men	0.46 (0.16, 0.75)	0.16	0.08	0.0003
Living conditions				
Alone vs. housemates (GR)	1.02 (0.81, 1.22)	0.11	0.19	0.001
Pets vs. housemates (GR)	0.65 (0.20, 1.09)	0.22	0.07	0.003
Housemates (BR) vs. housemates (GR)	0.36 (−0.08, 0.75)	0.20	0.04	0.071
Current work situation				
Unemployed vs. working externally	−0.07 (−0.38, 0.45)	0.17	−0.10	0.610
Working at home vs. working externally	−0.02 (−0.23, 0.42)	0.12	−0.03	0.801
Home, unable to work vs. working externally	0.08 (−0.24, 0.72)	0.19	0.11	0.599

Multiple linear regression model (95% bias-corrected and accelerated CI reported in parentheses). Confidence intervals and standard errors based on bootstrapping samples (1000 iterations). *ANSH* advice to not shake hands, *GR* good relationship, *PR* poor relationship.

Longing for touch was found to increase significantly with the duration of the regulations. Longing for touch was not associated with the severity of the regulations. Thus, the type of regulation that was in effect at the time of testing (advice not to shake hands, social distancing, lockdown, or complete lockdown), did not seem to modulate the level of longing for touch that was reported by participants. With respect to the socio-demographic factors, longing for touch was significantly associated with living conditions. Participants who lived alone or with pets reported to be significantly more touch deprived than participants who lived with housemates which whom they had a good relationship. Participants who lived with housemates with whom they had a bad relationship did not report higher levels of longing for touch than participants who lived with housemates with whom they had a good relationship (see Table 7.3). There was a significant association between longing for touch and gender, with men reporting lower levels of longing for touch than women and individuals who identified as non-binary.

Table 7.3. Mean longing for touch scores for living conditions

Living condition	Mean	Std. deviation
Living alone	8.55	1.71
Living with pets	8.38	2.37
Living with housemates and poor relationship quality	7.71	2.26
Living with housemates and good relationship quality	7.30	2.41

7.3.2 Perceived pleasantness of touch

7.3.2.1 Manipulation check

Prior to the main analysis, a manipulation check was conducted to determine whether participants scored higher on the touch perception questionnaire after viewing the CT-optimal touch video compared to the CT non-optimal touch video. A paired t-test showed that the CT-optimal touch video ($M = 7.02$, $SD = 1.98$) was indeed rated as significantly more pleasant than the CT non-optimal touch video ($M = 3.37$, $SD = 1.96$), $t(1947) = -64.94$, $p < 0.001$.

7.3.2.2 Main analysis

Two multiple linear regressions were conducted with perception of CT-optimal and CT non- optimal touch as respective outcome measures. The level of longing for touch, the severity and the duration of COVID-related regulations were included as between-subjects factors. Gender and age were also included as

predictors in the model, to control for the potential influence of these variables. The first model was a significant predictor for the perceived pleasantness of the CT-optimal touch video, $F(8, 1858) = 42.59$ $p < 0.001$, $R2 = 0.16$. The regression coefficients can be found in Table 7.4.

Table 7.4. Regression coefficients with perceived pleasantness of CT-optimal touch observation as outcome measure

Model	B	Std. error	β	t	*p*
(Constant)	4.59 (4.19, 4.99)	0.20	–	22.77	< 0.001
Longing for touch	0.28 (0.24, 0.31)	0.02	0.33	14.82	< 0.001
Duration of regulations	0.00 (−0.00, 0.01)	0.00	0.010	0.35	0.730
Regulation severity					
ANSH vs. complete lockdown	−0.49 (−1.17, 0.18)	0.34	−0.03	−1.44	0.150
Social distancing vs. complete lockdown	−0.54 (−0.84, −0.24)	0.15	−0.11	−3.52	< 0.001
Lockdown vs. complete lockdown	−0.61 (−0.84, −0.37)	0.12	−0.15	−5.12	< 0.001
Age	0.02 (0.02, 0.03)	0.00	0.18	8.09	< 0.001
Gender					
Non-binary vs. men	−0.30 (−1.63, 1.04)	0.68	−0.01	−0.44	0.661
Women vs. men	−0.02 (−0.23, 0.19)	0.11	−0.04	−0.19	0.848

Multiple linear regression model (95% CI in parentheses). *ANSH* advice to not shake hands.

The perceived pleasantness of the CT-optimal touch video significantly increased as the level of longing for touch (see Figure. 7.1) and age increased. Participants in complete lockdown also perceived the CT-optimal touch video to be significantly more pleasant than those who were under social distancing measures and those in lockdown. There was no difference in pleasantness ratings of CT-optimal touch videos between participants who were advised not to shake hands and participants who were in complete lockdown. The perceived pleasantness of the CT-optimal touch video was not significantly associated with the duration of regulations, nor gender.

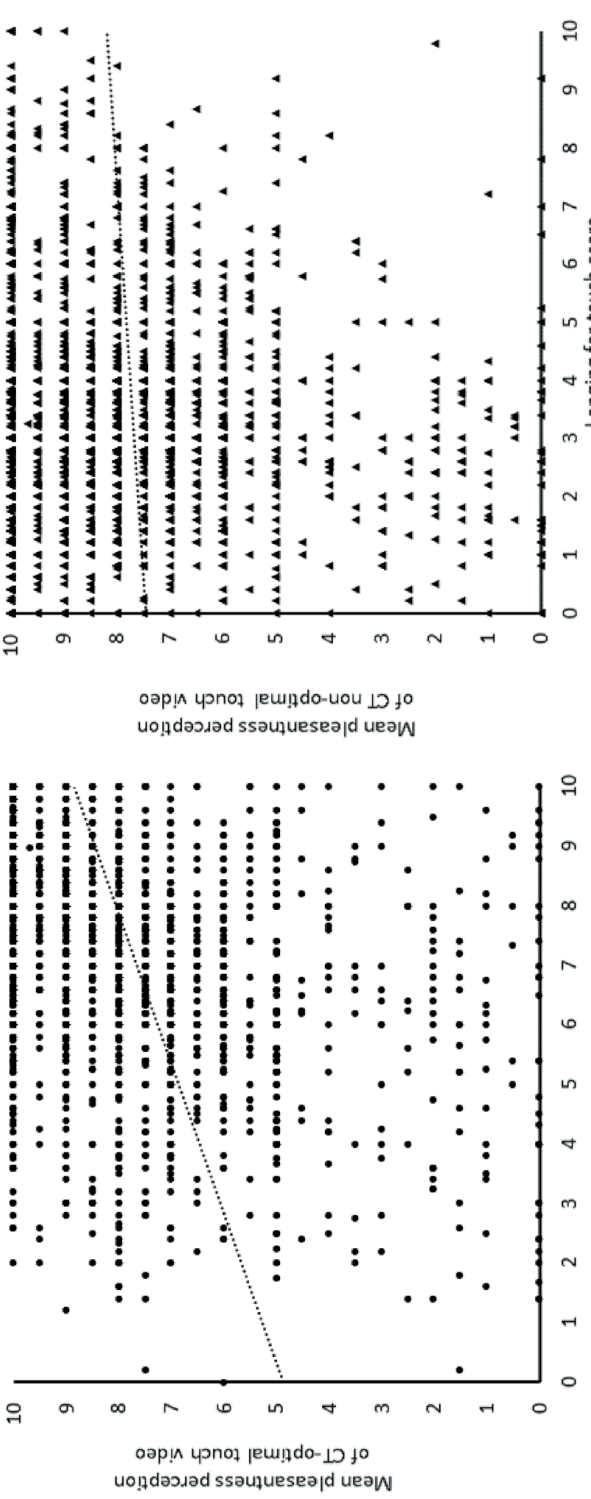

Figure 7.1. The relation between longing for touch and pleasantness perception of CT-optimal and CT non-optimal videos
The left panel depicts the individual data points and relation between longing for touch and pleasantness perception of the CT-optimal video. The right panel depicts the individual data points and relation between longing for touch and pleasantness perception of the CT non-optimal video.

The second model significantly predicted the perceived pleasantness of the CT non-optimal touch video, $F(8, 1852) = 6.84$, $p < 0.001$, $R2 = 0.03$. The regression coefficients can be found in Table 7.5.

Table 7.5. Regression coefficients wit perceived pleasantness of CT non-optimal touch observation as outcome measure

Model	B	Std. error	β	t	*P*
(Constant)	3.62 (3.19, 4.05)	0.22	–	16.41	< 0.001
Longing for touch	0.08 (0.04, 0.12)	0.02	0.10	4.09	< 0.001
Duration of regulations	−0.00 (−0.01, 0.00)	0.00	−0.00	0.12	0.100
Regulation severity					
ANSH vs. complete lockdown	−0.38 (−1.13, 0.36)	0.38	−0.03	−1.01	0.315
Social distancing vs. complete lockdown	−0.77 (−1.10, −0.45)	0.17	−0.16	−4.64	< 0.001
Lockdown vs. complete lockdown	−0.50 (−0.76, −0.25)	0.13	−0.12	−3.89	< 0.001
Age	> 0.001 (−0.00, 0.00)	0.00	0.00	0.02	0.986
Gender					
Non-binary vs. men	−0.95 (−2.41, 0.51)	0.13	−0.03	−1.28	0.201
Women vs. men	−0.31 (−0.54, −0.10)	0.12	−0.06	−2.72	0.007

Multiple linear regression model (95% CI in parentheses). *ANSH* advice to not shake hands.

Pleasantness scores for the CT non-optimal touch video were significantly and positively associated with levels of longing for touch. In addition, participants in complete lockdown perceived the CT non-optimal touch video to be significantly more pleasant than those who were socially distancing and those in lockdown. There was no difference in pleasantness ratings of CT non-optimal touch videos between participants who were advised not to shake hands and participants who were in complete lockdown. Women perceived the CT non-optimal touch video to be less pleasant than men. Individuals who identified as non-binary did not differ from men in terms of pleasantness ratings for the CT non-optimal video. There was no significant association between pleasantness ratings of the CT non-optimal video and the duration of the regulations, and age.

7.4. Discussion

Interpersonal touch has been found to play an important role in social bonding and has a positive influence on mental health (Coan et al., 2006; Morrison et al., 2010). During the COVID-19 pandemic, several regulations have been in effect to prevent the virus from spreading. Restrictions such as quarantine, lockdown, and social distancing have decreased the frequency of touch interactions outside the own household, which could result in feelings of touch deprivation (Von Mohr et al., 2021). Previous work on touch deprivation shows a link between touch deprivation and altered perceived pleasantness of CT-optimal touch (Field, 2010; Sailer & Ackerley, 2019). However, these studies have not been conducted in a large community sample experiencing restrictions with respect to social interactions. The aim of the current study was therefore to investigate if individuals report feelings of longing for touch under COVID-19 regulations, which factors contribute to longing for touch and if the level of longing for touch is associated with pleasantness perception of touch.

To assess if participants felt touch deprived, we asked them to indicate on a ten-point scale whether they would like to receive less touch/touch others less (0) or receive more touch/touch others more (10). On average participants scored 7.70, implying that participants longed for touch at the time of testing, as only a score of 5 would reflect a perfect balance between touch wish and touch frequency. Our findings are in accordance with the recent findings by Von Mohr et al. (2021), who also report a craving for touch during COVID-19 in their sample, especially with respect to professional and friendly touch, and to a lesser extent with respect to intimate touch. As we do not have longing for touch scores of our sample before the COVID-19 pandemic, we cannot draw any conclusions with respect to how the pandemic has impacted longing for touch scores. In other words, at this point we do not know whether the longing for touch score of 7.70 that we report here reflects a (significant) increase in feelings of longing for touch. However, a pre-COVID-19 study of Beßler et al. (2020) showed that over 70% of the healthy individuals in their sample reported that they experienced a longing for touch. So, it appears that even in a society in which there are no restrictions with respect to social interactions, individuals experience a discrepancy between the amount of touch they would want to receive and the amount of touch they actually receive. Interestingly, in our sample 82.9% of the participants reported that experienced a longing for touch. Although a direct statistical comparison between our post-COVID-19 longing for touch scores and the pre-COVID-19 longing for touch scores reported by Beßler et al. (2020) is not possible, we cautiously suggest that the restrictions

following from the COVID-19 pandemic have had a negative impact on the level of longing for touch reported in the community.

In addition, we investigated which sociodemographic variables were associated with variability in longing for touch scores. The results showed that higher levels of longing for touch were linked to a longer duration of COVID-19 regulations. This is in line with the recent work of Von Mohr et al. (2021) who also found that longing for touch is associated with the duration of COVID-19 and social distancing regulations. We further extend the findings by Von Mohr et al. (2021) by showing that not only the duration of the COVID-19 regulations is associated with higher levels of longing for touch but also the living situation of the participants. Participants who lived alone or who lived with pets reported higher levels of longing for touch than participants who lived with housemates with whom they had a good relationship. These findings are in accordance with recent work by Field et al. (2020), who also showed that living situation correlated with longing for touch. We did, however, not observe a difference in longing for touch levels between participants who lived with housemates with whom they had a bad relationship and participants who lived with housemates with whom they had a good relationship. Participants living with housemates might have had more opportunities to engage in human touch interactions compared to participants living alone or with pets. Nevertheless, participants living with housemates still reported to feel touch deprived at time of testing. Even participants living with housemates with whom they had a good relationship still had a longing for touch score of 7.30 (on a ten-point scale). This might be explained by findings of Von Mohr et al. (2021), who reported that under COVID-19 regulations individuals seem to especially crave friendly and professional touch. This highlights the importance of touch interactions with a variety of touch partners, e.g. significant others, but also friends or colleagues, for maintaining a satisfying balance between the need for touch and touch frequency. Participants who lived with housemates might thus still have craved touch interactions with individuals outside their household.

It should be noted that our regression model explained almost 10% of the variation in longing for touch. We included a limited amount of variables and it is clear that (multiple) other factors might also impact longing for touch. Future studies are needed to construct a complete and coherent overview of which variables determine how much one craves touch.

The second aim of our study was to explore the relation between longing for touch and the perceived pleasantness of observing touch during COVID-19. Participants watched short touch videoclips and rated the pleasantness of these videoclips. We specifically investigated which factors were associated with the

appraisal of touch observation. We found a positive association between longing for touch and pleasantness ratings for both CT-optimal and CT non-optimal touch videoclips, indicating that participants who longed for touch more reported higher levels of pleasantness when observing touch. This might be explained by top-down mechanisms such as social and contextual factors that have been found to be involved in the perception of CT-optimal touch (Banerjee et al., 2021; McGlone et al., 2014). It could be that the restrictions in social interaction increased our desire to be touched which led to a higher appraisal of touch. In addition, appraisal of CT-optimal touch is also linked to activation of brain areas involved in the reward system (India Morrison, 2016), it could be that in our study increased pleasantness ratings of touch reflect an increased activation of the reward system. A parallel can be drawn here with work focusing on the positive relation between food deprivation and the subjective appraisal of high-calorie foods (Goldstone et al., 2009). Similarly, craving touch might make the observation of touch more appealing. This explanation fits with our finding that not only CT-optimal touch videoclips were rated as more pleasant when longing for touch increased, but that the same pattern was observed for videoclips depicting CT non-optimal touch. It should however be noted that the explained variance for pleasantness ratings of CT-optimal touch videos was 16%, while the explained variance was only 0.3% for CT non-optimal touch videos. Nevertheless, a potentially interesting hypothesis following from this line of reasoning is that even forms of touch that do not necessarily activate CT-afferents may become more desirable when there are fewer opportunities to receive touch. To further explore this, future studies could focus on investigating how the perception of specific types of physical interactions (i.e. a handshake or an accidental brush) changes as longing for touch increases.

Our findings are in contrast with previous work that indicated that touch deprived participants experienced CT-optimal touch as less pleasant than participants who were not touch deprived (Sailer & Ackerley, 2019). Sailer and Ackerley (2019) suggest that infrequent CT-optimal touch experiences shape the interpretation and hedonic evaluation of those experiences. The contrasting findings between our study and that of Sailer and Ackerley (2019) might be explained by the fact that Sailer and Ackerley (2019) conducted an in person study, in which participants were actually touched, while we conducted a study in which participants observed videos depicting touch. Although observation of touch and being physically touched are different, earlier studies focusing on touch observation did show that observing CT- optimal touch activates the same brains regions as being physically touched (Lee Masson et al., 2018). Moreover, when observing touch videos, participants rated CT-optimal touch videos as

more pleasant than CT non-optimal videos (Willemse et al., 2016), similar to what is typically found in in person touch experiments. This suggests that top-down mechanisms also play an important role in the perceived pleasantness of CT-optimal touch. Future studies in which the interplay between longing for touch and pleasantness perception of both observed and physical touch is investigated could shed further light on this issue.

An alternative explanation for the contrasting findings between our study and that of Sailer and Ackerley (2019) might be found in the different social circumstances under which the studies were conducted. The study by Sailer and Ackerley (2019) was conducted in a society with no restrictions on social interactions. As such their participants were potentially touch deprived as a result of, for example, a limited social network or limited amount of touch partners. Indeed Sailer and Ackerley (2019) report that the majority of their touch deprived group did not have a partner and/or child(ren), while the majority of their control group did. In contrast, in our study participants' social network did not necessarily change, but the opportunity to engage in touch interactions with their social network did change as a result of the pandemic. As such, it could be that in the study of Sailer and Ackerley (2019) different social and contextual factors, such as the setting in which the study took place influenced the appraisal of CT-optimal touch.

We furthermore found a link between age and pleasantness perception of CT-optimal touch observation. This is in line with previous observations showing that pleasantness ratings for CT-optimal touch increase with age (Sehlstedt et al., 2016). We also found that participants in a complete lockdown perceived both CT-optimal and CT non-optimal touch videos to be more pleasant than those who were socially distancing and those who were in lockdown. Although this effect is not necessarily unexpected, it might not be entirely driven by the level of restrictions, as we also observed that pleasantness ratings of both CT-optimal and CT non-optimal touch videos were not different for those who were advised not to shake hands and those in complete lockdown. This could however be due to an unbalanced number of participants across each category of regulation severity. Less than 2% of our sample indicated that in their country of residence the only restriction in effect was an advice not to shake hands. A more likely explanation for higher pleasantness ratings of touch videos by those in a complete lockdown may be related to cultural differences. The majority of the participants in a complete lockdown lived in Italy. This is considered to be a high-contact culture in which, as recent research suggests, CT-optimal touch is more prevalent (Sorokowska et al., 2021). We therefore speculate that perhaps a combination of more severe COVID-19 regulation and living in a high contact

culture both have resulted in higher levels of observed touch pleasantness. It should however be noted that in our study we only asked participants to indicate which restrictions were in place at the time of participation, but we did not ask participants to indicate whether they indeed adhered to these regulations. The results with respect to pleasantness perception of touch videos and regulation severity should thus be interpreted with caution.

Even though pleasantness perception of touch videos appeared to be predicted by regulation severity, we did not find a link between regulation severity and longing for touch. Thus, regulation severity seemed to predict how pleasant participants rated the touch videos, but it did not predict how much participants longed for actual touch. This is a remarkable findings for which we do not have a clear explanation at this point.

Another limitation of the current study is that we did not take different types of social touch and interaction partners into account, which could have provided us with more information regarding the way in which individuals feel touch deprived. Von Mohr et al. (2021) did distinguish between professional, friendly, and intimate touch and showed that the difference in touch frequency pre- and post-COVID-19 was largest for friendly touch. However, the participants also reported that they craved intimate touch most and that this increased with duration of the COVID-19 regulations. These findings highlight the complexity of our need for touch and how this may impact feelings of touch deprivation.

To conclude, our results demonstrate that an increased duration of COVID-19 regulation is associated with higher levels of longing for touch in the community. It seems that individuals who live alone or who live with pets suffer from the higher levels of longing for touch, compared to individuals who live with housemates. In addition, longing for touch appears to be related to touch pleasantness perception. We found that higher levels of longing for touch were linked to a more pleasant perception of videoclips showing both CT-optimal and CT non-optimal touch. Thus, individuals who long for touch more find it more pleasant to watch videoclips showing interpersonal touch. We suggest that fewer opportunities to engage in touch may potentially increase the hedonic value ascribed to touch stimuli, similar to an increased liking of high calorie foods when food deprived. Our study contributes to the understanding of the factors that are associated with longing for touch and how this links to touch perception in (healthy) adults. By doing so, this study also provides new insights into the wider consequences of COVID-19-related public health measures.

Author contributions

All authors made substantial contributions to the conception and design of the work. J.K., A.M. and G.T. executed the experiment. L.M. and B.H. analyzed and interpretated the data. L.M., C.D. and A.K. wrote the main manuscript. C.D. and A.K. supervised. A.K. and B.H. managed the revisions. All authors gave final approval for publication and agree to be held accountable for the work performed therein.

Competing interests

The authors declare no competing interests.

Additional information

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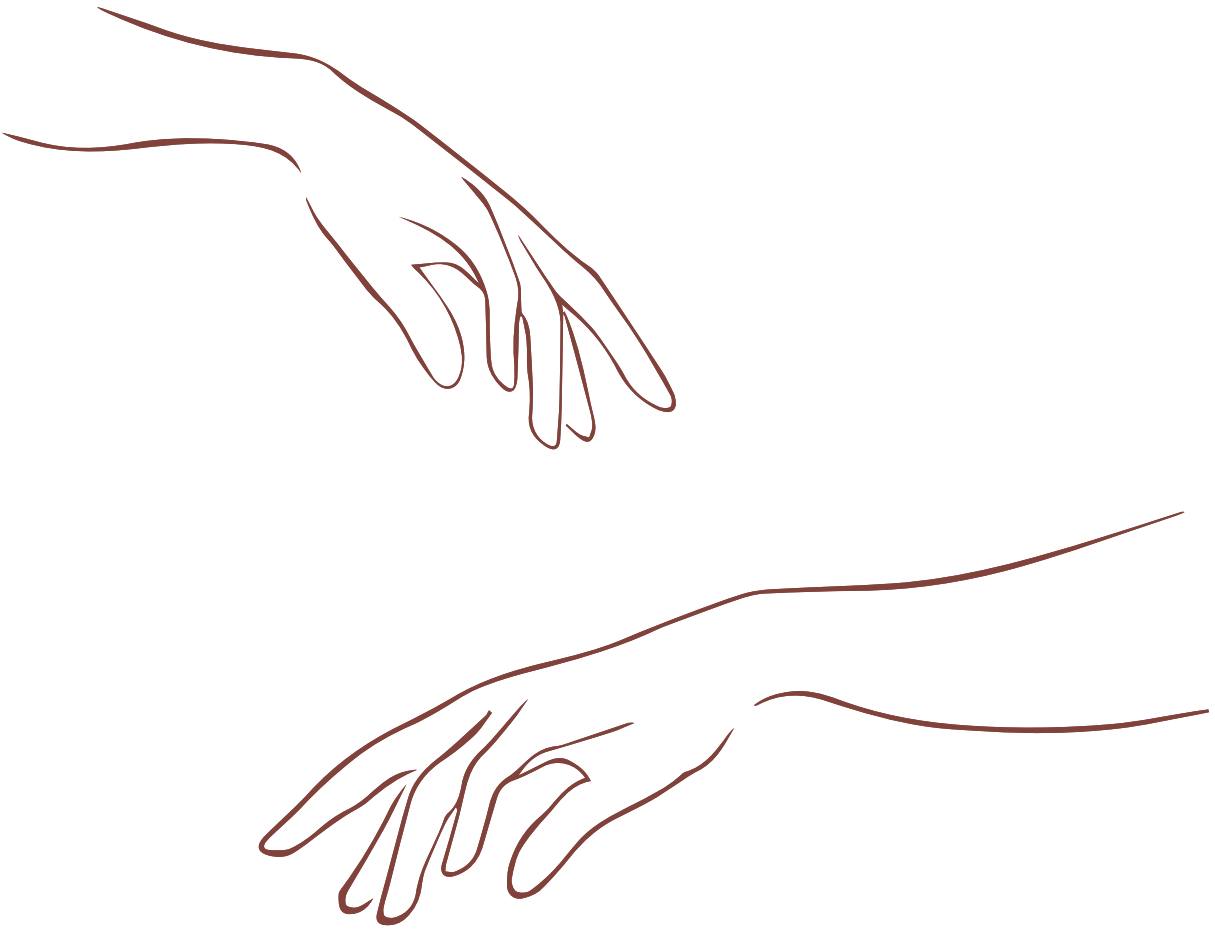
Chapter 8



General Discussion

8.1. Aim of the thesis

Pain and itch are two of our somatosensations which can cause serious discomfort (Dhand & Aminoff, 2014; Vogt & Sikes, 2000). However, for itch and (chronic) pain a sufficient treatment is still lacking (Bicket & Mao, 2015; Fowler & Yosipovitch, 2019). Therefore, searching for an effective treatment is warranted. Interestingly, previous research shows that CT-optimal touch, slow gentle stroking of the skin with a velocity of about 3 cm/s, can ameliorate acute pain (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017; Lu & Perl, 2003; Olausson et al., 2010; von Mohr, Krahé, et al., 2018). As CT-optimal touch can ameliorate acute pain, it is important to investigate whether CT-optimal touch could also influence chronic pain and itch. Therefore, one of the aims of the thesis was to investigate whether CT-optimal touch can ameliorate chronic pain and itch experience as well. Furthermore, if CT-optimal touch can ameliorate chronic pain, the feasibility of implementing CT-optimal touch in daily-routine was also investigated.

Importantly, touch automatically generates a shift of attention towards the stimulated site (Chapman, 2009). In addition, attention has shown to be a distractor from pain (Bascour-Sandoval et al., 2019). Therefore, previously found effects of CT-optimal touch on pain might rely partially on attentional effects. Besides these attentional effects, the location of the touch application might influence the pain ameliorating effect of CT-optimal touch as well. It is currently unknown whether there is a difference in effectiveness between applying CT-optimal touch directly at the pain location or at another bodily location. If we want to implement CT-optimal touch as a treatment for chronic pain it is necessary to investigate this difference. Especially, because CT-fiber density is not evenly distributed across the body (Ackerley, Carlsson, et al., 2014) and the locations were CT-fiber density is highest are not always similar to where chronic pain is felt (Cohen et al., 2021). The third aim of this thesis subsequently was to investigate if tactile attention and touch application site influence the pain ameliorating effect of CT-optimal touch.

In addition, we also questioned whether CT-optimal touch perception is related to how often we receive touch. During the COVID-19 pandemic social distancing measures were implemented to prevent the virus from spreading (Verity et al., 2020). These social distancing measures could influence how often we receive or provide touch. The fourth aim of the thesis consequently was to investigate if a large community sample was feeling touch deprived during the COVID-19 pandemic and if so, whether this influenced how we observe CT-optimal touch.

Interestingly, CT-optimal touch mostly elicits a pleasant sensation and is therefore also referred to as affective touch (Craig, 2009). The possible effects of CT-optimal touch on chronic pain and itch could be related to activation of the CT-fiber system but might also be a consequence of the affective or pleasant experience of the stimulus. The first can be considered as a bottom-up influence, while the latter is more top-down regulated (Elias & Abdus-Saboor, 2022). Therefore, I will also discuss in paragraph 8.3 whether there is a relationship between the ameliorating effect of CT-optimal touch and its perceived pleasantness. If this relationship is not found, a differentiation between CT-optimal touch and affective touch should be considered.

8.2. Study findings

To fully understand the mechanisms underlying CT-optimal touch and its interaction with pain processing, we first developed a model of the possible interaction(s) between these two somatosensations. This is described in **chapter 2**. Previous research into the neurophysiology of CT-optimal touch shows that CT-fibers convey signals to the dorsal horn of the spinal cord and from thereon to the thalamus, the anterior and posterior insula, anterior cingulate cortex (ACC), orbitofrontal cortex, medial prefrontal cortex, amygdala, hippocampus and hypothalamus (McGlone et al., 2014; Sailer et al., 2016). The neurophysiology of the medial pain system shows a clear overlap in (supra)spinal regions with the CT-system, which could indicate a relationship between these two types of somatosensory systems. This is supported by several behavioral studies showing that CT-optimal touch can reduce acute pain in healthy individuals (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017). Moreover, studies into the neurophysiology of the pain ameliorating function of CT-optimal touch show that there might be two ways through which CT-optimal touch modulates pain (Gursul et al., 2018; Lu & Perl, 2003; von Mohr, Krahé, et al., 2018). These are integrated in the novel model we provided (see Figure 8.1). One way is mediated by an inhibitory spinal mechanism, which relies on a specific inhibitory connection related to CT-afferent input, preventing nociceptive input from reaching (sub) cortical brain regions involved in pain processing. The other way relies on a downregulatory mechanism within the insula and ACC, which are important for the affective and motivational components of pain.

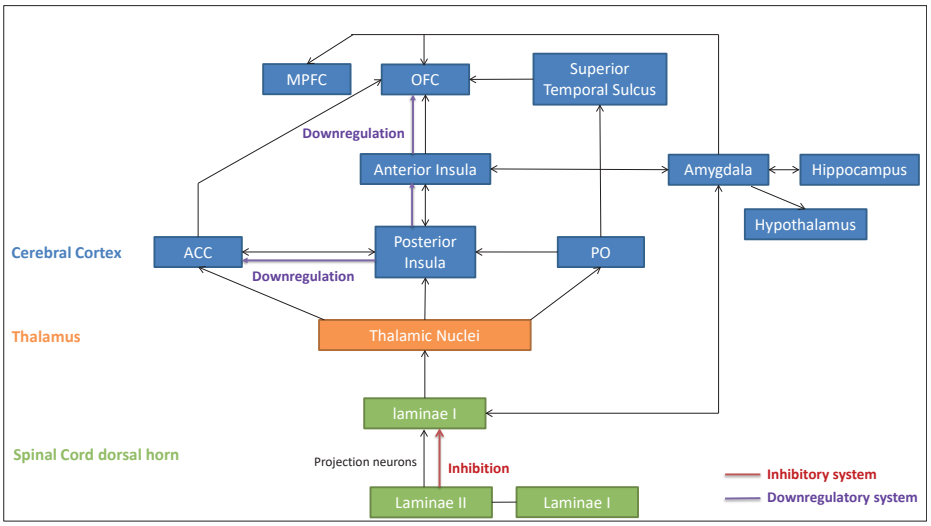


Figure 8.1. Novel model illustrating two possible ways CT-optimal touch modulates pain; through an inhibitory system and a downregulatory system

This novel model describing the interaction between CT-optimal touch and pain has been the foundation of my thesis and the studies described in **chapters 3 through 6**. As mentioned in the introduction of this thesis, not only CT-optimal touch and pain interact with each other, but also pain and itch share a clear connection. Based on the connections and clear overlap in (supra)spinal regions involved in these three somatosensations, we investigated whether CT-optimal touch can also influence itch experience in **chapter 3**. In this study, itch was induced electrically for 20 min. We used a within-subject design in which 61 participants received CT-optimal touch and CT non-optimal touch on the same arm as where itch was induced. Results show that both types of touch significantly reduced itch compared to baseline. Importantly, CT-optimal touch had an additional significant relieving effect compared to CT non-optimal touch. This effect started after 2 min of stroking and increased up till 6 min, hereafter the effect stabilized but still persisted. Furthermore, CT-optimal touch was perceived as significantly more pleasant than CT non-optimal touch. Yet, itch amelioration was shown to be independent of the perceived pleasantness.

As described, previous studies show that CT-optimal touch can ameliorate acute pain experience in healthy individuals (Gursul et al., 2018; Habig et al., 2017; Krahé et al., 2016; Liljencrantz et al., 2017; Lu & Perl, 2003; von Mohr, Krahé, et al., 2018). As studies show that chronic pain is a highly disabling disease on its own, the prevalence in Europe alone is already 21 – 40% (Todd et al., 2019) and an adequate treatment remains elusive (Bicket &

Mao, 2015), we wanted to investigate whether CT-optimal touch could also ameliorate chronic pain. The aforementioned studies have all been performed on healthy individuals. However, in order to investigate whether CT-optimal touch can be used as a new treatment for chronic pain, it is necessary to study its effects in a clinical population. Currently, there is only one experimental study that investigated the effect of CT-optimal touch on chronic pain in a clinical population (Di Lernia et al., 2020). Even though this study shows that CT-optimal touch reduced chronic pain, this study was performed in a lab-setting and if we wanted to know whether CT-optimal touch can be used as a treatment it is necessary to investigate this outside the lab.

We investigated this by using a longitudinal design in which touch was applied at home by the partner of the participants. This study, in which Parkinson patients suffering from chronic pain participated, is described in **chapter 4** and **chapter 5**. As chronic pain is highly undertreated in Parkinson's Disease (PD) (Edinoff et al., 2020) and it seems that the medial pain system is overactive resulting in chronic pain (Antonini et al., 2018), we hypothesized that CT-optimal touch might be effective in reducing chronic pain in this patient group. One of the participants of this study suffered from a burning pain of which the symptoms seemed similar to neuropathic pain. As neuropathic pain can affect how touch is perceived (Jones et al., 2003), this was officially an exclusion criteria of this study. However, as this was not formally diagnosed and the participant did perceive touch, we decided that he was eligible for participation. As this participant had a different response to CT-optimal touch compared to the other participants of this study, we decided to describe the results of this participant separately in a case report which is **chapter 4** of this thesis. This participant started to feel less pain after 2 days of CT-optimal touch administration, at the end of the CT-optimal touch week his pain had disappeared. In addition, the pain diminishing effect of CT-optimal touch persisted even after the administration of CT-optimal touch had stopped. Here, we speculate that CT-optimal touch modified an overactive pain system to its normal state. Interestingly, the participant did not perceive CT-optimal touch and CT non-optimal as pleasant, but CT-optimal touch was still effective in ameliorating his chronic pain experience.

In **chapter 5,** the results are described for the total sample of this study. Results of 18 participants suffering from PD and chronic pain show that CT-optimal touch as well as CT non-optimal touch ameliorate the chronic pain experience. Furthermore, CT-optimal touch has an additional immediate relieving effect and it is perceived as more pleasant. Interestingly, in this study the pain ameliorating effect of CT-optimal touch was also independent of its perceived pleasantness. As CT-optimal touch has an additional immediate

relieving effect and is perceived as more pleasant than CT non-optimal touch, we suggest that it might be used when immediate pain relief is needed. This is feasible, because this study also showed that CT-optimal touch can be easily applied by a partner and can be implemented as daily routine.

Based on the results of the studies described in **chapter 4** and **chapter 5**, it appears that CT-optimal touch can ameliorate chronic pain in PD. As described in **chapter 2**, CT-optimal touch might ameliorate pain through two mechanisms. Based on this knowledge we speculate that the pain amelioration described in **chapter 4** might rely more on the peripheral inhibitory pathway as this participant suffered from a burning chronic pain in his hands and CT-optimal touch was applied in an alternating manner on both the forearms. On the other hand, the participants described in **chapter 5** mostly suffered from musculoskeletal pain in the back and CT-optimal touch was also applied on the forearm. Therefore, pain amelioration might rely more on the top-down regulation at the level of the insula. So, based on these results we cannot determine whether CT-optimal touch should be applied on the pain site or application can be done on another body part. To study this we used a paradigm from Fidanza et al. (2021), who also investigated the effect of CT-optimal touch on pain experience. In our experiment, discussed in **chapter 6**, we induced pain by providing participants with repetitive ascending and descending heat stimulation. By doing so, temporal summation of second pain (TSSP), also referred to as wind-up pain, was induced. This relies on activating C-nociceptors, which is also linked to central sensitization, which in addition is an underlying mechanism of chronic pain (Staud et al., 2007). While TSSP was induced, 36 participants underwent three conditions; CT-optimal touch, CT non-optimal touch and a Tapping condition. Furthermore, touch was applied ipsilateral to where the pain was induced and contralateral to the pain induction side. Results showed that the Tapping condition did not reduce TSSP, meaning that tactile attention alone cannot reduce pain. CT-optimal touch was effective in reducing TSSP compared to CT non-optimal touch and tapping the skin. In addition, this effect was independent of touch application site. It therefore appears that CT-optimal touch can also be applied on a different body part than where the pain is located, which is highly relevant for implementing CT-optimal touch as a treatment.

The studies within my thesis show that receiving CT-optimal touch can have beneficial effects on chronic pain and itch experience. Previous studies also show that CT-optimal touch can have a positive influence on mental health (Tiffany Field, 2019). During the COVID-19 pandemic several social distancing regulations were implemented, which resulted in limited opportunities to engage in social touch. Therefore, in **chapter 7** we were interested in

investigating if these regulations led to feelings of touch deprivation and if so, would this influence the way we observe CT-optimal touch. To investigate this, we conducted an online survey which contained questions regarding the COVID-19 regulations, touch deprivation and participants reported the perceived pleasantness of videos depicting CT-optimal- and CT non-optimal touch. Results of 2348 participants showed that 87% of the sample reported feelings of touch deprivation, which significantly increased with the duration and severity of the social distancing regulations. Participants who reported higher feelings of touch deprivation rated CT-optimal touch and CT non-optimal touch as significantly more pleasant compared to participants who felt less touch deprived. In addition, participants rated the CT-optimal touch videos as more pleasant than the CT non-optimal touch videos. Here, we show that people did feel touch deprived during the COVID-19 pandemic. Importantly, feeling touch deprived is associated with increased perceived pleasantness of observed touch. We suggest that this leads to a higher desire for touch, similar to that of craving high calorie food when on a strict diet (Goldstone et al., 2009). As previous studies show that when CT-optimal touch is observed the same brain regions are activated when physically receiving touch, it appears that observing touch activates the same top-down pleasantness mechanism as actually receiving touch (Willemse et al., 2016). It might be that the increased pleasantness of observing touch also reflects increased perceived pleasantness when physically receiving touch.

To conclude, these studies show that CT-optimal touch can ameliorate chronic pain to a larger extent than CT non-optimal touch and adds to existing literature on the effect of CT-optimal touch on acute pain (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018) and chronic pain (Di Lernia et al., 2020). In addition, CT-optimal touch can also effectively reduce itch experience. Furthermore, in general, except for the participant described in **chapter 4**, CT-optimal touch is perceived as pleasant. Moreover, when the ability to provide or receive touch is limited, people feel touch deprived and this influences the way we observe touch. So, these studies show that CT-optimal touch can have several beneficial effects and that frequently receiving touch is important.

8.3. Should we differentiate between CT-optimal touch and affective touch?

As described in the introduction, Vallbo et al. (2009) introduced the *affective touch hypothesis* which states that the functional role of the CT-fibers is to convey pleasant touch. Since the inception of this hypothesis, CT-optimal touch and affective touch are often used interchangeably (even in our own literature). This suggest that the CT-fibers are inherently connected to the affective appraisal of touch. However, as even Vallbo et al. (2009) already described, the pleasant perception of touch is not solely based on activation of the CT-fibers. This is further substantiated by recent research of Case et al. (2023) which show that the affective and pleasant perception of touch also relies on the Aβ-fibers. Furthermore, research in mammals shows that grooming or even rubbing flippers is used to provide affective and social support (Gallace & Spence, 2010; McGlone et al., 2014). In humans affective and social support is often provided by handholding, a hand on the shoulder or a hug (Tiffany Field, 2019). These types of touch have a strong affective and often pleasant component similar to CT-optimal touch. However, these types of touch are unlikely to activate the CT-fibers (Meijer et al., 2022).

Based on the current knowledge of the CT-system and its relationship with tactile pleasantness, during my PhD I started to wonder if a differentiation between CT-optimal touch and affective touch might be necessary. A similar idea has very recently been suggested by Schirmer et al. (2023). These authors stated that the affective appraisal of touch is a higher-order process which can also be elicited by other types of touch rather than through CT-optimal touch alone, e.g. faster stroking or massage, which is in line with the study of Case et al. (2023).

In relation to the topic of the current PhD thesis, apparently, the pain ameliorating effect of CT-optimal touch and perceived pleasantness may be independent of each other. This is further substantiated by our studies discussed in **chapter 3 through 6**. Here, in general we did not find a relationship between the ameliorating effect of CT-optimal touch and the pleasantness ratings. This might show that the ameliorating effect of CT-optimal touch is based on activation of the CT-system rather than pleasantness related analgesic effects (Elias & Abdus-Saboor, 2022). This is in line with the proposed model on the interaction between CT-optimal touch and pain processing, which shows that the CT-system can interact with pain through a bottom-up and top-down mechanism. As CT-optimal touch appears to interact on bottom-up and top-down levels, I argue that when CT-optimal touch is applied on the same location as where pain or itch is experienced it seems likely that the CT-system interacts

more peripherally on the level of the spinal cord i.e. the bottom-up mechanism. In **chapter 3** the effect of CT-optimal touch on itch was investigated. Based on our model on the interaction between pain and the CT-system and the spinal inhibitory connection between pain and itch (Davidson & Giesler, 2010), we expect that there is also peripheral spinal interaction between CT-optimal touch and itch. As CT-optimal touch was applied on the same arm as where itch was induced, it could be that the relieving effect on itch relied more on the bottom-up inhibitory pathway. A similar argument can be made for the study in **chapter 4**, in which this patient suffered from a burning painful sensation in his hands and touch was applied in an alternating manner on both the lower forearms. As we did not compare this to applying CT-optimal touch on a different body part and we only used behavioral measures I can only speculate here.

In contrast, most of the participants in **chapter 5** suffered from musculoskeletal pain in their back. As touch was applied on the lower forearm, touch application was on a different body part than the pain location. Here, it might be that the pain ameliorating effect of CT-optimal touch relies more on the top-down regulatory mechanism between the insula and the ACC. This top-down system differs from top-down pleasantness related analgesics as this system is driven by activation of the CT-system. In contrast, top-down pleasantness related analgesics are also related to several other forms of social touch e.g. handholding, massage which do not activate the CT-system (Elias & Abdus-Saboor, 2022).

In addition, in **chapter 6** we did apply CT-optimal touch on the same body part and on a different body part from where TSSP was induced. Here, we showed that CT-optimal touch is effective in reducing TSSP and that this effect appears independent of touch application site. Meaning that applying CT-optimal touch on the pain location is as effective as applying touch on a different bodily location. This effect was also independent from the perceived pleasantness of CT-optimal touch.

Taken together, this shows that the ameliorating effect of CT-optimal touch can rely on bottom-up and top-down mechanisms, but these appear independent of higher-order top-down pleasantness modulation. I hereby tentatively suggest that this thesis, as well as recent literature (Case et al., 2023; Schirmer et al., 2023), shows that CT-optimal touch and affective touch might not be considered one and the same process, which should be kept in mind for future work into CT-optimal touch.

8.4. Implications for clinical practice and research

The studies described in this thesis provide (further) evidence for the itch and pain-relieving effect CT-optimal touch has, this is important as the current treatment is still insufficient (Bicket & Mao, 2015; Fowler & Yosipovitch, 2019). In **chapter 4** and **5** the first longitudinal study into the effects of CT-optimal touch on chronic pain is discussed. Here, we show promising results. Even more so as touch was applied solely by the partner. This has been done before by von Mohr, Krahé, et al. (2018) but in a lab-setting. During our study, participants and their partners subjectively reported to prefer CT-optimal touch compared to CT non-optimal touch as it seemed to reduce the chronic pain experience more and was also perceived as more pleasant. This is supported by the additional immediate effect CT-optimal has on the chronic pain experience of PD patients. In addition, during the study a total of 28 touch applications needed to be done and none of the participants reported to have missed any of these. This, in my opinion, shows that participants and their partners were not only committed to applying touch, but it was also feasible to perform touch when scheduled. As applying CT-optimal touch appears feasible during a longitudinal study with fixed touch moments, it might be easy to implement in one's own daily-routine. Furthermore, we also showed in an experimental study that the pain ameliorating effect of CT-optimal touch was independent of touch application site. This suggests that CT-optimal touch does not have to be applied on the same body part as where (chronic) pain is felt. This is highly relevant for the implementation of CT-optimal touch as a treatment for chronic pain. Especially because body parts with a high density of CT-fibers are often not similar to where chronic pain is experienced (Ackerley, Carlsson, et al., 2014; Cohen et al., 2021). In addition, chronic pain can also be felt internally around the organs which we cannot be reached by touching the skin (Bicket & Mao, 2015). Hereby, we provide a first step in the development of CT-optimal touch as a new additional non-pharmacological treatment for chronic pain. However, as this is the first and only study in which CT-optimal touch is investigated in a treatment like protocol, an additional study is needed in which the effect of CT-optimal touch on chronic pain can be compared with CT non-optimal touch in a Randomized Control Trial. If this results in similar findings, it is important to share these results not only within academia but also within clinical practice and society. As CT-optimal touch is shown to be easy to apply by a partner, it is also very feasible to be used in clinical practice. Furthermore, physicians, physiotherapist and neuropsychologist can easily recommend and demonstrate the usage of CT-optimal touch.

Moreover, our study focused on chronic pain in PD but there are also many other patient groups suffering from chronic pain. As CT-optimal touch has an immediate relieving effect in the PD patient group, it is necessary to investigate this in other chronic pain patients as well. One could think of other neurodegenerative diseases in which chronic pain is a symptom i.e. Alzheimer's Disease or Multiple Sclerosis (de Tommaso et al., 2016; Scherder et al., 2003), but also fibromyalgia in which pain is as key symptom (Vierck, 2006). Furthermore, ageing is also highly associated with chronic back pain and osteoarthritis and since the general population is getting older, more people will be vulnerable to developing chronic pain (Schwan et al., 2019).

In addition to the effect of CT-optimal touch on pain, we also show here that CT-optimal touch can relief itch. This is promising as itch is highly prevalent in dermatological diseases and in post-burn wounds (Chung et al., 2020; Weisshaar, 2016). The study in **chapter 3** is, as far as I know, the only study into the effect of CT-optimal touch on itch, however we induced itch electrically which has its limitations as this is not a suitable way to induce itch for everybody (Yuan et al., 2016). Another way to induce itch is by the usage of cowhage. Cowage is a plant-based substance inducing a mild itch, which is more similar to itchy sensations caused by dermatological diseases or insect bites (Andersen et al., 2017). Furthermore, research shows that cowage-induced itch can be used as an experimental model for chronic pruritic diseases (Papoiu et al., 2011). Therefore, I propose to further expand research into the effect of CT-optimal touch on itch and induce itch by using cowhage. If CT-optimal touch is also effective in reducing cowhage induced itch, this could be a foundation for investigating CT-optimal touch in patient groups suffering from chronic itch.

Besides studying CT-optimal touch in a clinical population and using behavioral measures to report pain experience, much is still unknown regarding the processing of CT-optimal touch and the underlying mechanisms of its interaction with pain processing. A few studies into the effect of CT-optimal touch on acute pain used EEG, LEP's and fMRI (Gursul et al., 2018; Habig et al., 2017; Krahé et al., 2016; von Mohr, Krahé, et al., 2018). As the above-mentioned studies focus on acute pain, the neurophysiology of CT-optimal touch and its effect on chronic pain has not been investigated yet. To study this, I propose to use the design of **chapter 6**, which induces TSSP related to central sensitization, and use EEG or LEP's to map the neurophysiology behind the pain ameliorating effect of CT-optimal touch and to use EEG in patient studies.

Finally, we also showed that many people feel touch deprived during the COVID-19 pandemic (**chapter 7**). Furthermore, a very recent study of ours shows that it seems that people did not only feel touch deprived during the COVID-19

pandemic but also feel touch deprived in a society without social restrictions (Hasenack, Meijer, van Harmelen, et al., 2023). This shows that many people do not receive the amount of touch they desire. Importantly, we also show that feeling touch deprived has negative consequences for our general well-being (Hasenack, Meijer, Kamps, et al., 2023). This further emphasizes the importance of receiving touch frequently.

8.5. Overall conclusion

In this thesis I aimed to investigate whether CT-optimal touch can ameliorate pain and itch in healthy individuals as well as in Parkinson patients suffering from chronic pain. I created a novel model, used experimental studies, a case-report and a longitudinal study to understand the underlying mechanisms of CT-optimal touch and its interaction with pain processing.

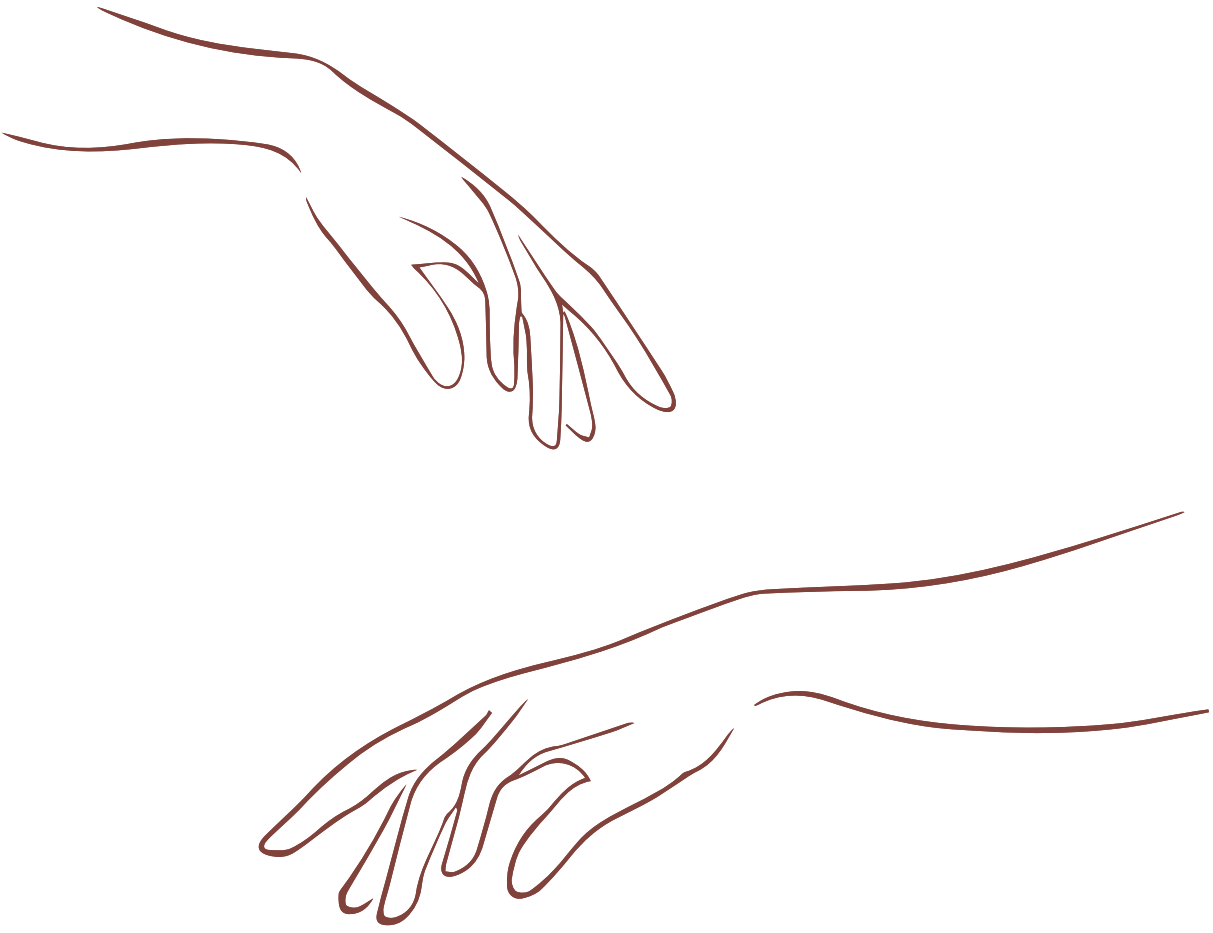
I show that CT-optimal touch can ameliorate chronic pain, that it might be used when immediate pain relief is needed and that it is feasible to implement in daily-routine. Furthermore, CT-optimal touch can also reduce electrically induced itch. In addition, I show that the ameliorating effect of CT-optimal touch is independent of the perceived pleasantness. This further emphasizes that it is necessary to differentiate between CT-optimal touch and affective touch, which is substantiated by Case et al. (2023) and Schirmer et al. (2023).

Furthermore, the results of an online study showed that people who feel touch deprived, report to observe touch as more pleasant. We also show that this has negative consequences for our general well-being (Hasenack, Meijer, Kamps, et al., 2023). As feeling touch deprived can have a negative impact on our mental health, this is relevant for the post-COVID-19 period as well. It also further emphasizes the importance of receiving touch frequently.

Taken together, this thesis further substantiates the importance of promoting receiving as well as providing CT-optimal touch as it appears to have many beneficial effects. Important first steps of implementing CT-optimal touch as a new non-pharmacological pain treatment are provided here as well. Expanding our current knowledge on the neurophysiology behind this type of touch and its interaction with pain and itch is a necessity for our further understanding.

8

Chapter 9



Nederlandse Samenvatting

Op zoek naar iemand die mij kan begeleiden
om te helpen mijn pijn te bestrijden
Een zachte aai hier en daar
over mijn huid en haar
Deze snelheid is goed bevonden
precies 3 centimeter per seconde!

Tast is een van onze zintuigen, welke zich als eerste ontwikkelt in de baarmoeder (Fagard et al., 2018). Tast is belangrijk voor het lokaliseren, discrimineren en identificeren van stimuli die zich op onze huid bevinden. Er werd lange tijd gedacht dat tast een primair discriminerende rol had en dat stimuli grotendeels worden verwerkt door zenuwbanen die informatie snel naar de hersenen kunnen sturen, de gemyeliniseerde Aβ-vezels (McGlone et al., 2014). Twintig à dertig jaar geleden kwam hier verandering in toen Nordin (1990) een andere specifieke vezel vond die tast input verwerkt, namelijk de C-Tactiele – vezels of wel CT-vezels. Deze CT-vezels reageren op langzame zachte streling van de harige huid, met een optimale snelheid van 3 cm/s en een range van 1 – 10 cm/s (CT-optimale aanraking; Olausson et al., 2010). Wanneer de CT-vezels worden geactiveerd kan dit een aangenaam gevoel geven, het wordt daarom ook wel affectieve aanraking genoemd (Vallbo et al., 2009). De CT-vezels projecteren naar de insula; een hersengebied dat belangrijk is voor interoceptie (het waarnemen van signalen uit het lichaam, zoals het kloppen van het hart) en de affectieve aspecten van onze somatosensorische sensaties waaronder tast, pijn en jeuk (Craig, 2009).

Naast dat CT-optimale aanraking een aangenaam gevoel kan geven, laten recente studies zien dat deze vorm van aanraking ook acute pijn kan verminderen (Gursul et al., 2018; Habig et al., 2017; Liljencrantz et al., 2017; von Mohr, Krahé, et al., 2018). Dit is een belangrijke en interessante bevinding aangezien er op dit moment nog geen toereikende behandeling is voor chronische pijn (Bicket & Mao, 2015). Chronische pijn wordt gedefinieerd als pijn die langer dan 3 maanden aanwezig is en niet passend is bij het natuurlijk herstelproces (Świeboda et al., 2013). Naast pijn is er nog een andere sensatie die voor veel ongemak kan zorgen, namelijk jeuk (Dhand & Aminoff, 2014). Pijn kan invloed hebben op jeuk, hetgeen wij bijvoorbeeld kunnen zien wanneer je op de jeukende plek krabt. Aangezien CT-optimale aanraking acute pijn kan verminderen, pijn invloed heeft op jeuk én voor zowel jeuk als chronische pijn nog geen toereikende behandelingen zijn, zal binnen dit proefschrift worden onderzocht of CT-optimale aanraking ook jeuk en chronische pijn kan verminderen.

Aangezien we uit eerder onderzoek weten dat CT-optimale aanraking een aangenaam gevoel kan opwekken (Vallbo et al., 2009), vroegen wij ons af of de waarneming van CT-optimale aanraking afhankelijk is van hoe vaak we deze aanraking krijgen. Gedurende de COVID-19 pandemie waren er meerdere maatregelen genomen om de spreiding van het virus tegen te gaan, waaronder *social distancing*. Deze maatregelen zouden invloed kunnen hebben op de hoeveelheid aanraking die iemand kan geven of ontvangen. Daarom hebben wij onderzocht of mensen gedurende de COVID-19 pandemie gevoelens van tastdeprivatie ervaarden én of dit invloed had op hoe zij CT-optimale aanraking waarnamen.

9.1. Bevindingen per hoofdstuk

In **hoofdstuk 2** wordt een door ons ontwikkeld theoretisch model beschreven, dit model geeft de interactie tussen het CT-systeem en pijnsysteem weer. Wanneer de CT-vezels worden geactiveerd, wordt het signaal eerst getransporteerd naar de dorsale hoorn van het ruggenmerg. Vanuit hier wordt het signaal doorgestuurd naar verschillende hersengebieden waaronder de insula, anterieure cingulate cortex (ACC) en mediale prefrontale cortex (McGlone et al., 2014; Sailer et al., 2016). Wanneer we kijken naar de verwerking van pijn, kunnen we onderscheid maken tussen twee systemen, het laterale- en het mediale pijnsysteem (Bell, 2018). Het laterale pijnsysteem is betrokken bij het lokaliseren en onderscheiden van de pijnlijke stimulus (Woller et al., 2017). Het mediale pijnsysteem daarentegen geeft informatie over de affectieve aspecten van de stimulus, met andere woorden: hoe ervaar ik deze stimulus (Vogt & Sikes, 2000)? Met name het mediale pijnsysteem laat veel overlap zien met het CT-systeem; dezelfde hersengebieden worden geactiveerd (onder andere de insula en ACC) en het signaal komt op dezelfde plek in de dorsale hoorn van het ruggenmerg binnen. Neurofysiologische studies laten zien dat er mogelijk twee manieren zijn waarop het CT-systeem kan interacteren met het mediale pijnsysteem, zodat het pijn kan verminderen. Deze twee manieren worden in ons model beschreven. De eerste berust op een inhiberend systeem in de dorsale hoorn van het ruggenmerg. De CT-vezels kunnen een specifieke inhiberende baan in de dorsale hoorn activeren welke ervoor zorgt dat het pijnsignaal niet verder verwerkt kan worden. Het tweede mechanisme bevindt zich in de hersenen en specifieker in de insula. Wanneer pijn wordt ervaren, activeert dit de insula en ACC. Het CT-systeem zorgt ervoor dat deze activatie wordt geremd waardoor er minder pijn wordt ervaren.

Dit model en de kennis over de interactie tussen CT-optimale aanraking en pijn zijn de basis geweest voor de studies in **hoofdstuk 3 tot 6** van dit proefschrift. Zoals eerder beschreven kan pijn invloed hebben op jeuk, het pijnsysteem inhibeert het jeuksysteem op het niveau van de dorsale hoorn van het ruggenmerg (Davidson & Giesler, 2010). We weten dus dat er een duidelijke connectie is tussen CT-optimale aanraking en pijn, tussen pijn en jeuk én dat dezelfde hersengebieden betrokken zijn bij deze somatosensorische sensaties. Om deze reden hebben wij in **hoofdstuk 3** onderzocht of CT-optimale aanraking invloed heeft op jeuk. Aan dit experiment hebben 61 participanten deelgenomen. Jeuk werd elektrisch geïnduceerd en participanten kregen op dezelfde arm 20 minuten lang CT-optimale aanraking en CT non-optimale aanraking. CT non-optimale aanraking is een snellere aanraking van 18 cm/s en activeert de CT-vezels niet. De resultaten laten zien dat beide aanrakingen de jeuk verminderden, echter had CT-optimale aanraking een significant sterker verminderend effect op de jeuk. Daarnaast werd CT-optimale aanraking als aangenamer ervaren dan CT non-optimale aanraking. Het jeuk verminderende effect van CT-optimale aanraking was onafhankelijk van de ervaren aangenaamheid van deze aanraking.

Zoals beschreven laten eerdere studies zien dat CT-optimale aanraking acute pijn kan verminderen (Gursul et al., 2018; Habig et al., 2017; Krahé et al., 2016; Liljencrantz et al., 2017; Lu & Perl, 2003; von Mohr, Krahé, et al., 2018). Gezien een toereikende behandeling voor chronische pijn nog niet gevonden is (Bicket & Mao, 2015) en de prevalentie van chronische pijn op dit moment in Europa al op 21-40% ligt (Todd et al., 2019), is het belangrijk om te onderzoeken of CT-optimale aanraking chronische pijn zou kunnen verminderen. Een aandoening waarbij chronische pijn veelvuldig voorkomt is de ziekte van Parkinson, 30-85% van de patiënten ervaart chronische pijn (Edinoff et al., 2020). Het is nog niet helemaal duidelijk waardoor chronische pijn bij de ziekte van Parkinson ontstaat. Onderzoeken laten wel zien dat het mediale pijnsysteem, belangrijk voor de affectieve aspecten van pijn, overactief is (Antonini et al., 2018). Een studie van Di Lernia et al. (2020) laat zien dat CT-optimale aanraking chronische pijn kan verminderen. Echter was deze studie uitgevoerd in een laboratorium en aanraking werd gegeven met behulp van een elektronisch apparaat. Daarnaast laat een eerdere studie naar het effect van CT-optimale aanraking bij acute pijn zien dat het effect sterker is wanneer een geliefde de aanraking geeft (von Mohr, Krahé, et al., 2018).

Op basis van deze informatie hebben wij een longitudinale studie opgezet waarbij het effect van CT-optimale aanraking op chronische pijn bij Parkinson werd onderzocht. Tijdens deze drie weken durende studie rapporteerden participanten eerst een week lang hun pijnbeleving, dit om per participant een

nulmeting te verkrijgen. Hierop volgde een week lang CT-optimale aanraking of CT non-optimale aanraking en daarna nog een week met één van de twee aanrakingen. Tijdens de aanrakingsweek kreeg de deelnemer tweemaal per dag 15 minuten lang één van de twee aanrakingen van zijn/haar partner. De aanraking werd altijd gegeven op de bovenkant van de onderarm, omdat hier voldoende CT-vezels aanwezig zijn (Watkins et al., 2021). In **hoofdstuk 4** beschrijven wij een van de deelnemers aan deze studie. Deze deelnemer rapporteerde een branderige pijn in beide handen, welke al meerdere maanden aanwezig was. Gedurende de laatste week van de studie kreeg deze deelnemer CT-optimale aanraking. Al binnen twee dagen verminderde de branderige pijn in zijn handen en aan het einde van de week was deze pijn volledig verdwenen. Dit effect hield zelfs stand nadat de deelnemer en partner waren gestopt met het geven van de aanraking. Het lijkt erop dat in dit geval CT-optimale aanraking het overactieve pijnsysteem van deze deelnemer weer heeft genormaliseerd waardoor de pijn is verdwenen. Opvallend was dat deze deelnemer CT-optimale aanraking niet als aangenaam ervaarde, maar het alsnog effectief was in het verminderen van de pijn.

In **hoofdstuk 5** wordt de longitudinale studie voor de overige 18 deelnemers besproken. Hier laten we zien dat zowel CT-optimale aanraking als CT non-optimale aanraking chronische pijn vermindert. Echter CT-optimale aanraking had een additioneel effect direct na de aanraking. Dit wil zeggen dat direct nadat een deelnemer 15 minuten CT-optimale aanraking had gekregen, ervaarde hij/zij minder pijn. Daarnaast werd CT-optimale aanraking als meest aangenaam beoordeeld. Er was geen samenhang tussen het pijnstillende effect van CT-optimale aanraking en de ervaren aangenaamheid. Deze studie laat zien dat CT-optimale aanraking ingezet zou kunnen worden wanneer directe pijnverlichting wenselijk is. Daarnaast was het voor alle deelnemers haalbaar om het geven van de aanraking te implementeren in hun dagelijkse routine, het zou daarom gebruikt kunnen worden als laagdrempelige pijnbehandeling die thuis uitgevoerd kan worden.

Op basis van de studies beschreven in **hoofdstuk 4** en **hoofdstuk 5** zou CT-optimale aanraking chronische pijn kunnen verminderen. Voordat CT-optimale aanraking kan worden ingezet als nieuwe behandeling is het belangrijk om te onderzoeken welke factoren invloed kunnen hebben op het pijn verminderende effect van CT-optimale aanraking. Eén van deze factoren zou tactiele aandacht kunnen zijn. Zodra iets of iemand ons aanraakt wordt onze aandacht direct naar de plek van de aanraking getrokken (Chapman, 2009). Onderzoek laat tevens zien dat door aandacht op iets anders te vestigen dan de ervaren pijn of aangedane plek we minder pijn ervaren (Bascour-Sandoval et

al., 2019). Het effect van CT-optimale aanraking op onze pijnbeleving zou dan ook deels kunnen worden verklaard door tactiele aandacht. Een andere factor die het effect van CT-optimale aanraking op pijn zou kunnen beïnvloeden, is de locatie van de aanraking. Wanneer CT-optimale aanraking op dezelfde plek wordt gegeven als waar men pijn ervaart, komen beide signalen op dezelfde plek in het ruggenmerg binnen en is activatie van het inhiberende systeem aannemelijker. Dit lijkt het geval voor de deelnemer beschreven in **hoofdstuk 4**, welke pijn in de handen rapporteerde en CT-optimale aanraking werd gegeven op de onderarm. Aan de andere kant hadden de 18 deelnemers beschreven in **hoofdstuk 5** met name last van rugpijn. Gezien CT-optimale aanraking ook hier op de onderarm werd gegeven en de locatie van de aanraking en de pijnklachten dus van elkaar verschilde, zou men hier verwachten dat het effect van CT-optimale aanraking meer berust op het remmende-mechanisme in de hersenen. In dit geval komen de signalen namelijk niet op dezelfde plek in het ruggenmerg binnen en komen de signalen pas samen in de hersenen, specifieker in de insula waar het remmende-mechanisme zich bevindt. Op basis van deze twee studies kunnen we dus niet concluderen of CT-optimale aanraking op of nabij de pijnlocatie moet worden gegeven of dat het ook effectief is wanneer het op een ander lichaamsdeel wordt gegeven.

Om deze twee factoren te onderzoeken hebben we een studie opgezet die in **hoofdstuk 6** is beschreven. Voor deze studie hebben we een experiment van Fidanza et al. (2021) als uitgangspunt genomen. In dit experiment werd pijn opgewekt door middel van warmte stimulatie, dit wordt ook wel t*emporal summation of second pain* (TSSP) genoemd. Met deze methode wordt een mechanisme geactiveerd dat vaak betrokken is bij chronische pijn en op deze manier kan bij gezonde mensen chronische pijn worden gesimuleerd. Tijdens het opwekken van TSSP ondergingen 36 proefpersonen drie condities; een conditie waarbij op de huid wordt getikt (deze conditie werd gebruikt als een vorm van tactiele aandacht), CT-optimale aanraking en CT non-optimale aanraking. De aanraking werd gegeven op de onderarm, zowel op de arm als waar pijn werd geïnduceerd als op de andere arm. De resultaten lieten zien dat CT-optimale aanraking effectiever is in het verminderen van de pijn vergeleken met CT non-optimale aanraking en het tikken op de huid. CT non-optimale aanraking was alleen effectief wanneer het op dezelfde plek als de pijn werd gegeven. Het tikken op de huid zorgde niet voor minder pijn. Deze studie laat zien dat tactiele aandacht pijn niet kan verminderen en kan de effecten van CT-optimale aanraking daarmee ook niet verklaren. CT-optimale aanraking is effectief in het verminderen van pijn zowel op de pijnlocatie als op de andere arm, echter was er geen verschil tussen deze condities. Dit betekent dat

CT-optimale aanraking zowel gegeven kan worden op de plek van de pijn als op een andere plek op het lichaam. Dit impliceert dat voor het behandelen van chronische pijn het wellicht belangrijker is een locatie te kiezen waar zich veel CT-vezels bevinden zoals de arm dan de exacte pijn locatie. Dit zou de toepassing in de klinische praktijk ook toegankelijker maken, aangezien er ook veel vormen van chronische pijn zijn waarbij de pijn zich meer intern bevindt en CT-optimale aanraking niet direct op de locatie kan worden gegeven (Bicket & Mao, 2015).

Bovengenoemde onderzoeken laten zien dat CT-optimale aanraking chronische pijn en jeuk kan verminderen. Daarnaast tonen eerdere onderzoeken aan dat CT-optimale aanraking een positieve invloed heeft op mentaal welzijn (Tiffany Field, 2019). Het is dus van belang om voldoende (CT-optimale) aanraking te krijgen. Gedurende de COVID-19 pandemie waren er *social distancing* maatregelen genomen om de spreiding van dit virus tegen te gaan, welke invloed konden hebben op de mogelijkheid om elkaar aan te raken. In **hoofdstuk 7** hebben wij daarom onderzocht of deze beperking leidde tot tastdeprivatie en zo ja, of dit invloed had op hoe wij CT-optimale aanraking waarnemen. Dit hebben wij onderzocht door middel van een online vragenlijst waarin werd gevraagd naar de mate van ervaren tastdeprivatie. Daarnaast kregen proefpersonen filmpjes te zien van iemand die CT-optimale aanraking en CT non-optimale aanraking kreeg. Resultaten van 2348 deelnemers lieten zien dat 87% tastdeprivatie ervaarden en dat dit samenhing met de duur en ernst van de *social distancing* maatregelen. Deelnemers die een hoge mate van tastdeprivatie rapporteerden beoordeelden de aanrakingsfilmpjes als aangenamer dan deelnemers die in mindere mate tastdeprivatie rapporteerden. Daarnaast werd de CT-optimale aanrakingsvideo als aangenamer beoordeeld dan de CT non-optimale aanraking. Dit onderzoek laat zien dat mensen inderdaad gevoelens van tastdeprivatie ervaarden tijdens de COVID-19 pandemie en dat dit samenhangt met hoe aangenaam we een aanraking vinden.

9.2. Implicaties en conclusie

De studies beschreven in dit proefschrift tonen aan dat CT-optimale aanraking jeuk en pijn kan verminderen. We hebben in deze studies tevens aangetoond dat er geen samenhang is tussen de ervaren aangenaamheid van CT-optimale aanraking en het pijn/jeuk reducerende effect. Dit is belangrijk omdat dit informatie geeft over de onderliggende processen die verantwoordelijk kunnen zijn voor het effect dat CT-optimale aanraking heeft op pijn en jeuk. Zoals beschreven wordt met CT-optimale aanraking het CT-systeem geactiveerd. Door het activeren van het CT-systeem kan de pijn worden geremd met als resultaat dat we minder pijn ervaren. Echter, er zijn ook andere processen die voor pijnvermindering kunnen zorgen. Een voorbeeld hiervan is het verminderen van pijn doordat we iets plezierig of aangenaam ervaren (Elias & Abdus-Saboor, 2022). Dit proces kan geactiveerd worden wanneer een aanraking als aangenaam wordt ervaren. Naast CT-optimale aanraking kan men dan denken aan massages of het prettige gevoel wanneer een naaste onze hand vasthoudt. Deze vormen van sociale aanraking kunnen ook pijn verminderen maar activeren de CT-vezels niet, en berusten dus op andere processen. Aangezien de onderzoeken in dit proefschrift laten zien dat het effect van CT-optimale aanraking op pijn en jeuk niet in verband staat met de ervaren aangenaamheid van deze aanraking zou voorzichtig geconcludeerd kunnen worden dat dit effect niet berust op pijnstilling door de aangenaamheid van de aanraking maar door de activatie van het CT-systeem.

Naast deze meer theoretische implicatie heeft dit proefschrift tevens een aantal klinische implicaties. Op dit moment is er voor chronische pijn en jeuk nog niet voor iedereen een toereikende behandeling (Bicket & Mao, 2015; Fowler & Yosipovitch, 2019). De longitudinale studie beschreven in dit proefschrift is de eerste waarbij er over een langere tijd wordt gekeken naar de effecten van CT-optimale aanraking op chronische pijn. Hier laten we zien dat CT-optimale aanraking chronische pijn kan verminderen. Tevens toont het onderzoek aan dat het haalbaar is CT-optimale aanraking te implementeren in iemands dagelijkse routine en dat partners de aanraking kunnen geven zonder intensieve training. Daarnaast gaven deelnemers en partners de voorkeur aan CT-optimale aanraking omdat zij deze als effectiever en aangenamer ervaarden. Dit is daarmee een belangrijke eerste stap naar het gebruiken van CT-optimale aanraking als behandeling. Mogelijk is een dergelijke laagdrempelige behandeling ook inzetbaar bij andere aandoeningen waar chronische pijn veel voorkomt zoals Alzheimer, Multiple Sclerosis en fibromyalgie (de Tommaso et al., 2016; Scherder et al., 2003; Vierck, 2006). Daarnaast worden mensen steeds

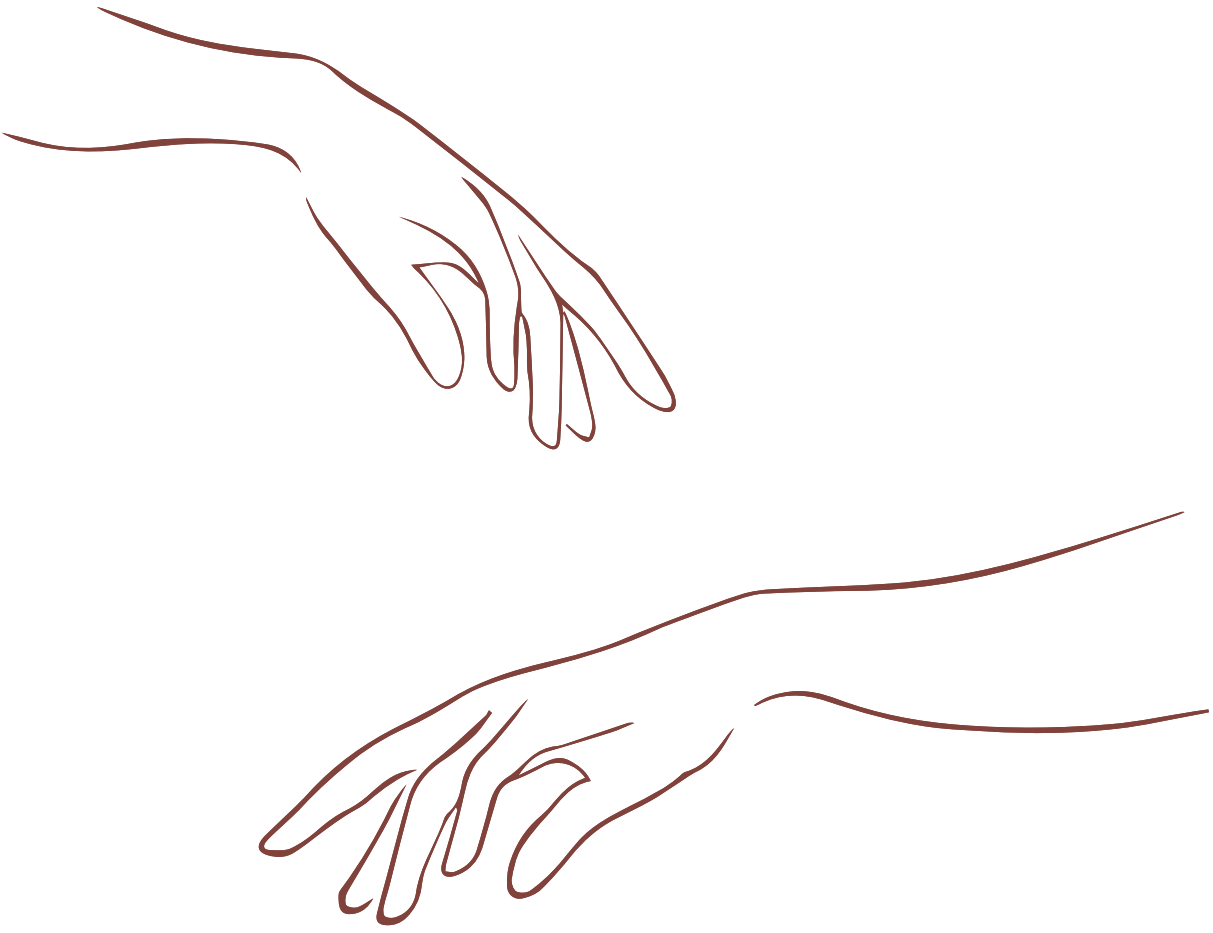
ouder en hangt chronische pijn samen met veroudering, naar verwachting zullen dus meer mensen lijden aan chronische pijn in de toekomst (Schwan et al., 2019). Naast chronische pijn is ook chronische jeuk een veelvoorkomende klacht, bijvoorbeeld bij huidaandoeningen zoals eczeem maar ook als gevolg van brandwonden (Chung et al., 2020; Weisshaar, 2016). Onze studie is voor zover we weten de eerste die heeft gekeken naar het effect van CT-optimale aanraking op jeuk, met positieve resultaten. Het is daarom wenselijk dat het onderzoek naar CT-optimale aanraking als behandeling van chronische pijn en jeuk wordt voortgezet.

Als we CT-optimale aanraking als behandeling willen gaan gebruiken is het belangrijk om te weten welke factoren invloed hebben op het pijnstillende effect. Een van deze factoren is de locatie van de aanraking. CT-optimale aanraking lijkt niet alleen effectief wanneer het op de plek van de pijn wordt gegeven maar ook wanneer het op een andere locatie dan waar de pijn zich bevindt wordt gegeven. Dit is zeer interessant aangezien dit suggereert dat het belangrijker kan zijn om CT-optimale aanraking te geven op een plek waar zich veel CT-vezels bevinden zoals op de arm dan op de plek van de pijn. Aangezien dit een eerste studie is waarin dit werd onderzocht, is het belangrijk om hier verder onderzoek naar te doen.

Naast deze duidelijk positieve effecten van CT-optimale aanraking op pijn en jeuk, zijn er meer positieve effecten van deze vorm van aanraking op mentaal en fysiek welbevinden (Tiffany Field, 2019). Het is daarom van belang voldoende aanraking te krijgen. Zo hebben wij in **hoofdstuk 7** aangetoond dat een groot deel van de bevolking tijdens de COVID-19 pandemie last had van tastdeprivatie, welke negatieve effecten had op ons mentaal welbevinden (Hasenack, Meijer, Kamps, et al., 2023).

Samengenomen laat dit proefschrift zien dat het belangrijk is dat we het geven en ontvangen van CT-optimale aanraking promoten, gezien het meerdere voordelen kan hebben op ons welbevinden. We hebben hier tevens de eerste stappen gezet in het implementeren van CT-optimale aanraking als nieuwe pijnbehandeling. Het verder uitbreiden van onze kennis over CT-optimale aanraking is daarvoor cruciaal.

Appendix



Acknowledgements (Dankwoord)

Acknowledgements (Dankwoord)

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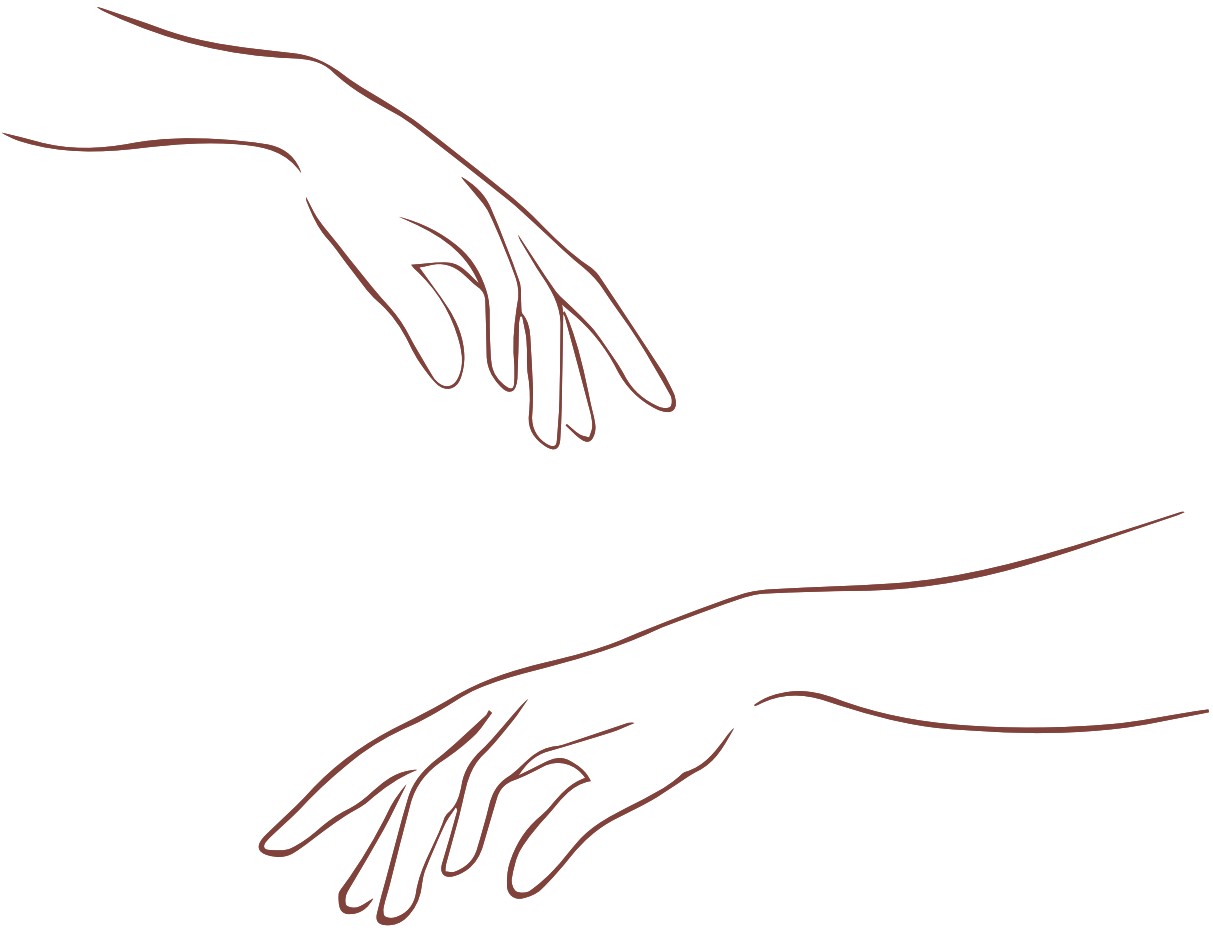
I will always be just a touch away!

Appendix



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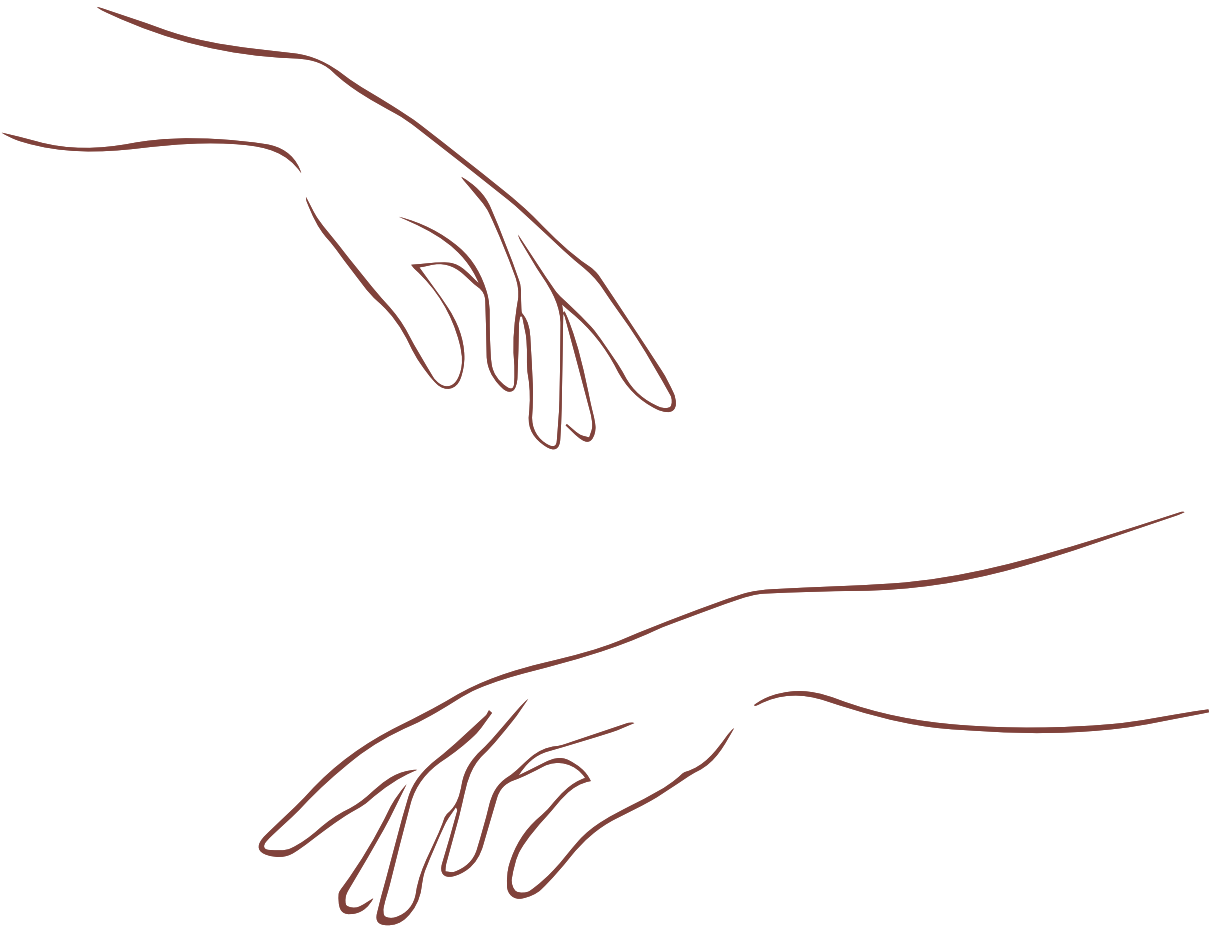
Appendix



List of Publications

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Meijer LL, Ruis C, Schielen ZA, Dijkerman HC, van der Smagt MJ (2024) CT-optimal touch and chronic pain experience in Parkinson's Disease; An intervention study. PLOS ONE 19(2): e0298345. https://doi.org/10.1371/journal.pone.0298345

Meijer, L.L., Baars, W., Ruis, C., Dijkerman, H.C., & van der Smagt, M.J. Spatial factors influencing the pain-ameliorating effect of CT-optimal touch: a comparative study for modulating temporal summation of second pain. Sci Rep 14, 2626 (2024). https://doi.org/10.1038/s41598-024-52354-3

Hasenack, B.*; Meijer, L.L.*, van Harmelen, A., Overvliet, K.E., & Keizer, A. Longing for touch post-COVID-19: current observations and future directions. Sci Rep 13, 22131 (2023). https://doi.org/10.1038/s41598-023-49113-1 *shared first author

Meijer, L.L., Ruis, C., van der Smagt, M.J., & Dijkerman, H.C. (2023). Chronic pain relief after receiving affective touch: A single case report. Journal of neuropsychology, 10.1111/jnp.12321. Advance online publication. https://doi.org/10.1111/jnp.12321

Hasenack, B.*; Meijer, L.L.*; Kamps, J.C.C.; Mahon, A.; Titone, G.; Dijkerman, H.C.; Keizer,A. Longing for Touch and Quality of Life during the COVID-19 Pandemic. Int. J. Environ. Res. Public Health 2023, 20, 3855. https://doi.org/10.3390/ijerph20053855 *shared first author

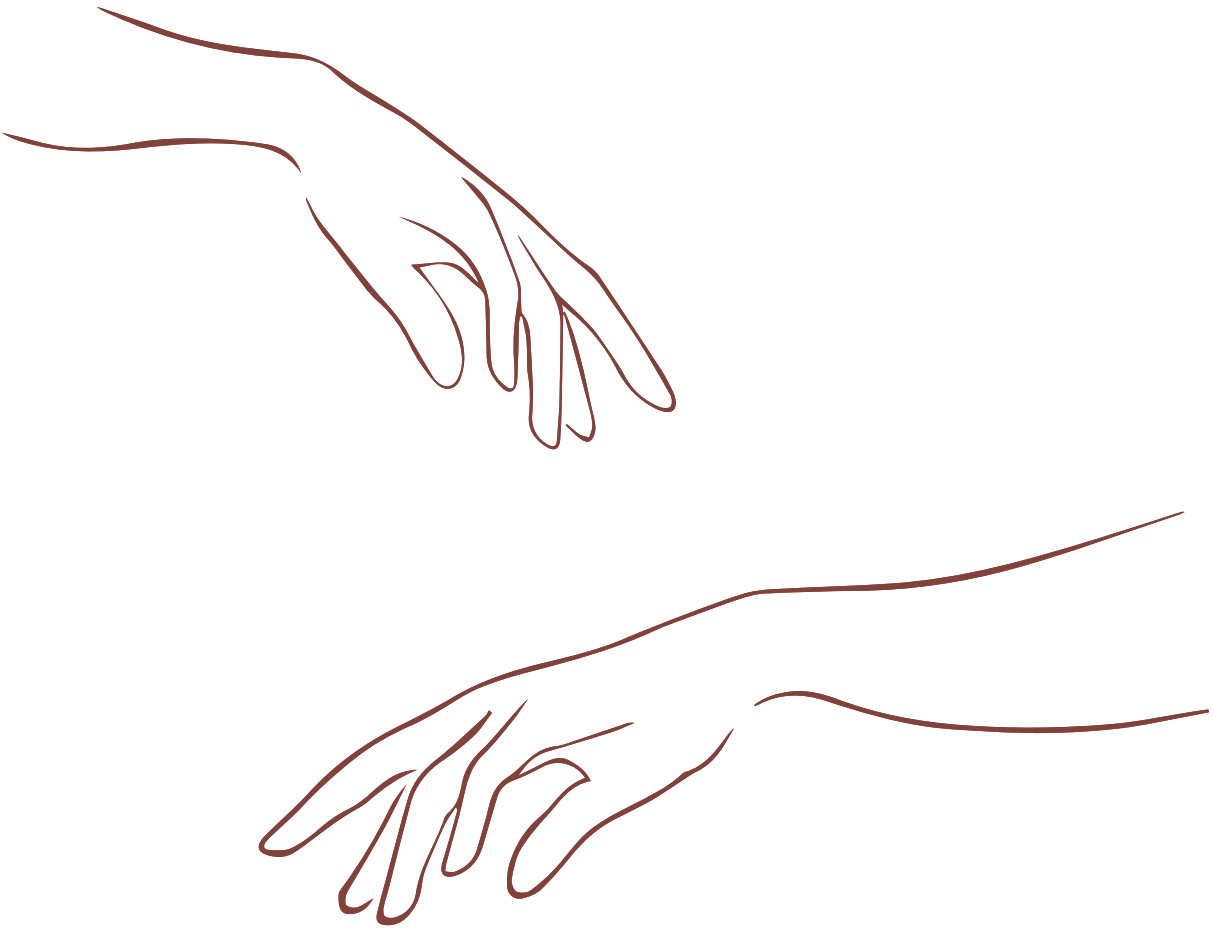
Meijer, L.L., Hasenack, B., Kamps, J.C.C., Mahon, A., Titone, G., Dijkerman, H.C., & Keizer, A. Huidhonger: De COVID-19-pandemie en de impact op interpersoonlijk fysiek contact (2022). Tijdschrift voor Neuropsychologie, 17 (3).

Meijer, L.L., Hasenack, B., Kamps, J.C.C., Mahon, A., Titone, G., Dijkerman, H.C., & Keizer, A. Affective touch perception and longing for touch during the COVID-19 pandemic. Sci Rep 12, 3887 (2022). https://doi-org.proxy.library.uu.nl/10.1038/s41598-022-07213-4

Meijer, L.L., Ruis, C., van der Smagt, M.J., Scherder, E.J.A. and Dijkerman, H.C. (2022), Neural basis of affective touch and pain: A novel model suggests possible targets for pain amelioration. J Neuropsychol, 16: 38-53. https://doi.org/10.1111/jnp.12250

Meijer, L.L., Schielen, Z.A., van Ree, K.Y., & Dijkerman, H.C. (2021). Affective Touch Reduces Electrically Induced Itch Experience. Frontiers in medicine, 8, 628020. https://doi.org/10.3389/fmed.2021.628020

Appendix



About the Author

About the Author

Larissa Meijer was born on the 27th of May 1992 in Haarlem. During high school her interest in science started to develop. She already knew that she aspired a job in which she could combine her interest in science, the human brain and clinical work. She started her bachelor's in psychology at the Erasmus University in Rotterdam, which focused on clinical psychology but from the beginning her plan was to do a masters in neuropsychology. However, Erasmus University did not offer this program, so she did a master in Neuropsychology at the Vrije Universiteit in Amsterdam which she successfully completed in 2015. After obtaining her master's degree she leaned more towards the clinical part of neuropsychology, but finding a job was difficult at that time. During her clinical internship she also had the opportunity to provide clinical lessons for healthcare workers. She really enjoyed teaching and applied for a job as junior lecturer at the department of Experimental Psychology of Utrecht University.

In 2016 she started as a junior lecturer. In the meantime, she was asked to work as a neuropsychologist at Nieuw Unicum, where she did her clinical internship. Even though she enjoyed working as a neuropsychologist, her job in academia triggered her previous and somewhat lost interest in science. She wanted to start a PhD and successfully wrote a grant application. In 2020 she officially started her PhD at the Dijkerman lab, which was finished September 2023. During her PhD she discovered that her future ambitions lie within academia. She applied for a job as Assistant Professor at the department of Experimental Psychology, she was hired and is fully enjoying this job since September 2023.