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When pain offset induces pleasure: A psychophysical and fMRI study

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When pain offset induces pleasure: A psychophysical and fMRI study

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Résumé

Introduction: Une stimulation nociceptive localisée peut produire une analgésie diffuse par un mécanisme endogène inhibiteur de la douleur (MEID). Des stimuli plaisants (e.g. musique) ainsi que le plaisir induit par l'interruption de la douleur peuvent également induire une analgésie. Pour cette raison, il est possible que l'analgésie causée par le plaisir (induite par l'arrêt de la douleur) soit un effet confondant dans le MEID. **Objectifs:** 1) Examiner la possibilité d'une relation entre le plaisir induit par l'arrêt de la douleur et le MEID et 2) Étudier l'interaction entre le plaisir et la douleur en examinant les activations/désactivations cérébrales *pendant* une stimulation nociceptive. **Méthodologie:** Étude 1) Le MEID a été mesuré (N=27) en administrant une chaleur nociceptive (thermode) avant et après le *test de l'eau froide.* Après une pause de 30 minutes, le *test de l'eau froide* a été réadministré pour mesurer le niveau de plaisir (0-100) induit par l'arrêt de la douleur (mesuré pendant 4 minutes). Étude 2) Un stimulus nociceptif (gel froid) a été administré (N=26) pendant une session d'IRMf. **Résultats:** Étude 1) L'arrêt du *test de l'eau froide* a induit une hypoalgésie avoisinant les 40%. Le MEID et le plaisir induit par l'interruption de la douleur n'étaient pas corrélés. Étude 2) Comparativement au stimulus neutre, le gel froid a induit une activation significative des régions de douleur (e.g. insula, precuneus) et une désactivation significative dans le gyrus frontal orbital moyen. **Discussion:** La désactivation du gyrus frontal orbital moyen illustre le débalancement de l'homéostasie pendant la stimulation douloureuse, qui est ensuite rétablit par l'augmentation du plaisir, suite à l'interruption de la douleur (effet compensatoire entre la douleur et le plaisir).

Mots clefs: ICPM, récompense, douleur, IRMf

Abstract

Background: A localized painful stimulation can produce diffused analgesia through the inhibitory conditioned pain modulation system (ICPM). Analgesia can also be induced by pleasant stimuli (e.g. music) or by the interruption of a painful stimuli (pleasant pain relief). Because pleasure has analgesic benefits, the effect of pleasant pain relief could be a confounding factor in ICPM. Furthermore, pain offset induces *activations* in reward regions, though results showing the *deactivation* of reward regions during pain onset have been inconsistent. **Objectives:** 1) investigate the possible relationship between pleasant pain relief and ICPM using psychophysical measures and 2) investigate cerebral activations/deactivations during pain onset. This will allow a better comprehension of the pain/reward interaction. **Methodology:** In study 1, ICPM was measured (N=27) by administering noxious heat (thermode) before and after the cold pressor test (CPT). After a 30 minutes break, the CPT was re-administered to measure pleasant pain relief (0-100) for 4 minutes. In study 2, a modified CPT (gel) was administrated (N=26) during an fMRI session to investigate cerebral activations/deactivations during pain onset. **Results:** In study 1, interruption of the CPT induced a mean pleasant pain relief of almost 40%. ICPM and pleasant pain relief did not correlate. In study 2, we found significant activations in the insula, the precuneus and the middle frontal gyrus and a significant deactivation in the medial orbital frontal gyrus during pain onset, when compared to the neutral stimulus. **Discussion:** Deactivation of reward regions illustrates the disruption in homeostasis caused by pain onset, which is later reinstated during pain offset (pleasant pain relief), therefore showing a compensatory effect. This allowed an enhanced comprehension of the *opponent process theory.*

Key words: ICPM, pleasant pain relief, reward, pain, fMRI

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Study 1 accepted by Pain research and Management

Study 2

List of abbreviations

ACC = Anterior cingulate cortex

aMCC = Anterior middle cingulate cortex

BDI = Beck depression inventory (BDI)

BPI = Brief Pain Inventory

BOLD = Blood oxygenated level dependent

CNS = Central nervous system

CPT = Cold pressor test

DLPFC = Dorsal lateral prefrontal cortex

fMRI = Functional magnetic resonance imaging

GLM = general linear model

ICPM = Inhibitory conditioned pain modulation

IAPS = International Association for the study of Pain

MCC = Middle cingulate cortex

MFG= Middle frontal gyrus

NAc = Nucleus accumbens

NRM = Nucleus raphe magnus

pACC = Pregenual anterior cingulate cortex

PAG = periaqueductal grey

PCC = Posterior cingulate cortex

pMCC = Posterior middle cingulate cortex

PRP = Pleasant relief of pain

RSC = Retrosplenial cortex

RVM = Rostral ventral medulla

sACC = Subgenual anterior cingulate cortex

SEM = Standard error of the mean

SHIPS = Snaith-Hamilton Pleasure Scale

STAI-S = State and Trait Anxiety Inventor-State subscale

SI = Primary somatosensory

SII = Secondary somatosensory

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Chapter 1. Introduction

1.1 Problem

Pain is considered a vital component for survival as it allows us to be aware of possible tissue damage in our body (Garland & Ph, 2013). In fact, pain is generally viewed as an unpleasant experience, both emotionally and physically, that humans tend to avoid. In turn, it is the main reason people seek medical attention (Shi, Langer, Cohen, & Cleeland, 2007). In accordance with the *International Association for the study of Pain* (IASP), pain is currently defined as a stressful and unpleasant sensory and emotional experience, that involves either potential or actual tissue damage. The main components of pain are sensory, affective and cognitive (Williams & Craig, 2016).

Pain may be beneficial when it serves for awareness and survival, but it becomes problematic when it is persistent and unrelieved, such as in chronic pain states (Fenton, Shih, & Zolton, 2015). Chronic pain is defined as pain that persists for longer than 6 months (Cheng & Rosenquist, 2018). Three main factors have been identified in playing a role in the development of chronic pain: (i) environmental factors (e.g. family abuse, history of pain), (ii) psychological factors (e.g. depression, anxiety) and (iii) individual predispositions (e.g. gender, age) (Marchand, 2008). Chronic pain affects 20% of people worldwide and has an estimated prevalence of 29% amongst Canadians over the age of 18 (Bonakdar, 2017; Cheng & Rosenquist, 2018; Tracey & Mantyh, 2007; Velly & Mohit, 2018). Furthermore, the total cost of pain treatment is estimated at 16,636 CAD per patient (Lalonde et al., 2014). Chronic pain causes therefore a major social and economic burden to both patients and society.

Chronic pain may also affect the psychological well-being of patients. For instance, up to 85% of people with chronic pain also suffer from severe depression (Cheng & Rosenquist,

2018; Sheng, Liu, Wang, Cui, & Zhang, 2017). Also, patients with chronic pain are 4 times more likely to have depression or anxiety when compared to non-chronic pain sufferers (Velly & Mohit, 2018). Because the cause of chronic pain remains unknown in many clinical cases, it is often accompanied by feelings of anger, helplessness and hopelessness (Tang & Crane, 2006). Consequently, the lifetime prevalence of suicidal ideation is common amongst these patients (Velly & Mohit, 2018).

Chronic pain also has physical consequences. Such consequences include muscles tension, difficulty in walking, loss of appetite, lack of energy and lack of sleep, which often all lead to the inability to work (Cheng & Rosenquist, 2018). A review composed of 43 studies on the functional consequences of pain over different chronic pain conditions, such as arthritis and fibromyalgia, has shown that 13 to 76% of chronic pain patients face loss of employment (Moore, Derry, Taylor, Straube, & Phillips, 2014).

Finally, patients with chronic pain tend to have a reduced quality of life (Abu Bakar et al., 2016; Lamé, Peters, Vlaeyen, Kleef, & Patijn, 2005). Quality of life questionnaires usually measure the impact of the illness on the emotional, social and physical functioning of the patient (Abu Bakar et al., 2016). Vast clinical observations show that chronic pain has major impacts on these three qualities of life domains (Lamé et al., 2005). Certain characteristics, such as pain intensity, pain frequency, duration of pain and the presence of other symptoms (e.g. nausea), are important predictors for reduced quality of life (Abu Bakar et al., 2016).

In brief, patients with chronic pain face psychological and physical consequences which may lead to disabilities in work, household and social functioning (Abu Bakar et al., 2016).

1.2 Types of Pain

One important step in diagnosis is identifying the type of pain the patient is experiencing. The three main categories of pain are nociceptive, neuropathic and functional pain (Marchand, 2008).

1.2.1 Nociceptive pain

Firstly, nociceptive pain is one of the most common types of pain and is caused by the activation of pain receptors (nociceptors) (Cervero, 1999; Steeds, 2009). Indeed, nociceptive pain can have a protective role in the human body as it can be triggered when potentially harmful stimuli are detected by nociceptors (Marchand, 2008). Nociceptive stimuli can be mechanical, thermal or chemical and can be detected in various parts of the body, such as skin, muscles, bones or internal organs (C. J Woolf, 1995). The typical description for this type of pain is aching or throbbing, which tends to worsen when a patient moves or coughs (Cheng & Rosenquist, 2018).

Nociceptive pain is divided in three subcategories: somatic, visceral and inflammatory (Cheng & Rosenquist, 2018; Marchand, 2008). 1- Somatic pain can be either superficial (at the surface of the skin) or deep (e.g. muscle pain). These types of pain can be caused by lacerations or fractures (e.g. surgical wound or broken bone) (Marchand, 2008). 2- Visceral pain is related to pain that is located on the viscera (e.g. gallbladder, appendix or heart). One important characteristic of visceral pain is that it is frequently irradiated pain. In simpler terms, visceral pain is often perceived in a different area than the actual damaged tissue, that is, it is poorly located and diffuse (Sikandar & Dickenson, 2012). A common example consists of the symptoms of a heart attack, where pain is diffused in the left arm and neck (Cheng & Rosenquist,

2018). 3- Inflammatory pain is a phenomenon associated with the healing process of injured tissues and is characterized by hypersensitivity to the injured area (Marchand, 2008). The inflammatory response can cause a heightened perception of pain to nociceptive stimuli (hyperalgesia). The inflammatory response includes swelling and redness on the injured area (Gyurkovska et al., 2011).

1.2.2 Neuropathic pain

Neuropathic pain refers to pain caused by a lesion or a disease affecting the peripheral nervous system (e.g. diabetes) or the central nervous system (e.g. brain trauma from tumours or strokes) (Cheng & Rosenquist, 2018). Neuropathic pain can be both spontaneous (not elicited by a stimulus) or non-spontaneous (elicited by a stimulus) (Cruccu & Truini, 2009). The latter is triggered by mechanical, thermal or chemical stimuli (Marchand, 2008). Damages to the nervous system can cause hyperalgesia and allodynia (pain sensitivity to non-nociceptive stimuli) (Borzan & Meyer, 2009). Some clinical characteristics that arise from neuropathic pain are burning pain, shooting pain, sensory deficit or pain to a light touch to the skin (Borzan & Meyer, 2009).

Neuropathic pain can be assessed clinically based on symptomatology and physical characteristics (Borzan & Meyer, 2009). Hence, the presence of characteristics such a burning, painful cold and electric shock accompanying the pain and the presence of symptoms such as tingling, pins and needles, numbness and itching in the same area as the arising pain are indicative of neuropathy (Borzan & Meyer, 2009). Finally, using touch and pinpricks, hypoesthesia (diminished sensitivity to stimuli) can be detected and allodynia can be detected using a light touch to the skin (e.g. brushing) (Cruccu & Truini, 2009).

1.2.3 Functional pain

The last category of pain is functional pain. This category classifies pain that has no known medical cause (Marchand, 2008). Indeed, when physicians are unable to identify a disease based on the group of symptoms given to them by the patient, the pain experienced is classified as functional pain (Schechter, 2014). Some disorders that fall into this category are fibromyalgia and irritable bowel syndrome (IBS) (Marchand, 2008). Fibromyalgia is characterized by chronic widespread pain and includes several symptoms such as fatigue, decreased physical functioning and tenderness (Wolfe et al., 2016). A diagnosis of fibromyalgia requires chronic pain to be present in at least 4-5 different regions (e.g. left arm, right arm, lower back, left hip, right hip and abdomen) and for the symptoms to be present for at least three months (Wolfe et al., 2016). The pain experienced can be of aching or cramping nature (e.g. headaches or stomach cramps). IBS is characterized by abdominal pain that can be tolerable to severe (El-Salhy, 2012). Symptoms include constipation or diarrhea, and in some cases, a combination of both. IBS diagnostic requires abdominal pain to be present for at least 6 months and the presence of symptoms such as abnormal stool frequency, abnormal stool shape and bloating (El-Salhy, 2012).

1.3 Components of pain

Pain is a multifaceted phenomenon and factors such as context, cognition, mood and attention, all have an influence on pain perception (Tracey & Mantyh, 2007; Tracey et al., 2002; Wiech, Ploner, & Tracey, 2008). Even when nociceptive stimuli are the same, patients may perceive pain differently due to these factors (M. P. Jensen et al., 2006). As previously

mentioned, pain perception is comprised of three main components; sensory, affective and cognitive (Williams & Craig, 2016).

1.3.1 Sensory

The first component of pain that will be discussed is the sensory-discriminative component. This component refers to the patient's ability to describe the intensity (mild to severe), the texture, the duration (for how long the pain has been ongoing) and the spatial characteristics of the pain (location) (Marchand, 2008). The latter two characteristics can be crucial in identifying the medical problem (M. E. Mendoza, Gertz, & Jensen, 2014). Localization is generally facilitated by asking the patient to perform different movements or by locating any tender areas that may increase pain perception. On the other hand, temporal characteristics allow the differentiation between acute, chronic, variable (pain always present but at different intensities) or intermittent pain (pain comes and goes) (M. E. Mendoza et al., 2014). Patients may use terms such as throbbing, aching, cramping or shooting to describe their experience (M. P. Jensen et al., 2006).

Pain can also be induced in experimental settings. Mechanical, thermal or chemical stimuli can be used to induce moderate pain to patients, who in turn are questioned about pain intensity (Marchand, 2008). These experiments can allow the identification of different sensory deficits such as hypoalgesia or hyperalgesia. Although the sensory-discriminative component allows patients to describe the pain, emotional components are important to take under consideration, as they may increase or decrease pain perception (Marchand, 2008).

1.3.2 Affective

In experimental and clinical settings, the affective component of pain is often referred to as pain unpleasantness (Leknes, Brooks, Wiech, & Tracey, 2008; Marchand, 2008). Emotional factors influencing pain perception include positive (e.g. happy) and negative (e.g. anxiety and depression) emotional states (M. E. Mendoza et al., 2014). Studies have shown that emotional factors alone can affect pain sensitivity and pain unpleasantness (Wiech & Tracey, 2009). However, positive and negative emotions tend to have a greater impact on the affective component of pain (pain unpleasantness) than on the sensory component of pain (pain intensity) (Villemure & Bushnell, 2002). Factors such as pleasant odours, music and emotionally pleasant pictures have been used to increase positive mood and thus decrease pain perception (Leknes & Tracey, 2008; Villemure & Bushnell, 2002). Conversely, factors causing a negative mood (e.g. viewing of negative images) has been shown to increase pain sensitivity and pain unpleasantness (Meagher, Arnau, & Rhudy, 2001; Villemure & Bushnell, 2002). Likewise, increased anxiety has also been found to cause increased pain intensity and pain unpleasantness (Ploghaus et al., 2001). Equally, treating anxiety has shown to reduce both pain and the need for analgesic medication (Hansen & Streltzer, 2005).

1.3.3 Cognition

Cognitive factors such as pain anticipation, pain catastrophizing, pain distraction and pain relief expectations, may modulate our painful experience by increasing or decreasing pain perception (Seminowicz & Davis, 2007). Firstly, pain anticipation has shown to cause increased pain perception (Fairhurst, Wiech, Dunckley, & Tracey, 2007). For instance, in a typical experimental procedure, participants received a warning cue before the application of the

noxious stimulus. This experiment showed a significative positive correlation between the level of pain anticipated during the anticipation cue and pain intensity during nociceptive stimulation ($r=0.62$, $p=0.02$) (Fairhurst et al., 2007). Likewise, several studies have observed a positive relationship between high levels of pain catastrophizing and increased pain intensity (Edwards, Bingham, Bathon, & Haythornthwaite, 2006; Tracey & Mantyh, 2007). Pain catastrophizing has been defined as an exaggerated perception of pain (threat, value or seriousness) that an individual attributes to their painful experience (Tracey & Mantyh, 2007). Furthermore, attention and distraction have opposite effects on pain perception. Although focused attention on pain has been shown to increase pain perception, pain distraction has been shown to be very useful in decreasing pain perception during painful procedures (Hansen & Streltzer, 2005; Palermo, Benedetti, Costa, & Amanzio, 2015). In fact, burn victims who were distracted using virtual reality reported significantly less pain during their treatment compared to patients receiving no distraction with their treatment (Hoffman, Patterson, Carrougher, & Sharar, 2001). This effect has also been tested in experimental settings. When participants were distracted by focusing their attention on a visual stimulus or a cognitive task (e.g. stroop task), sensory pain ratings were significantly reduced (Kenntner-Mabiala, Weyers, & Pauli, 2007; Moont, Crispel, Lev, Pud, & Yarnitsky, 2012). Finally, according to research on placebo analgesia, participants report reduced pain perception when they are informed a treatment will induce analgesia, even in the absence of actual treatment (Watson et al., 2009).

1.4 Pain Perception

As highlighted beforehand, mood and several cognitive factors can have an influence on the perception of pain (Tracey & Mantyh, 2007). On neurobiological grounds, the first step of pain perception lies in the activation of nociceptors in the periphery (Marchand, 2008).

1.4.1 Nociceptors and peripheral fibres

The trajectory leading to pain perception starts with the activation of the peripheral nociceptors. These nociceptors are free nerve endings of nerve fibres that are activated by nociceptive stimuli (Steeds, 2009). There are three main types of peripheral afferent fibres, Aβ, Aδ and C fibres (Marchand, 2008). Aβ and Aδ are both myelinated fibres and C fibres are unmyelinated. Aβ fibres participate in the transmission of non-nociceptive signals, such as a light touch or a vibration. Aδ and C fibres are the two fibres involved in the transmission of nociceptive signals. These sensory fibres are first order neurones (Kaiser, Haid, Shaffrey, & Fehlings, 2018). Aδ fibres react to thermal and mechanical nociceptive information, whereas C fibres are activated by mechanical, thermal and chemical information (Marchand, 2008). Since Aδ fibres are myelinated, they are responsible for the first pain response, a fast and sharp and pain sensation. Unmyelinated C fibres, on the other hand, are responsible for the second pain response. They transfer their information at a slower rate and produce the prolonged deep sensation of pain (Fenton et al., 2015; Marchand, 2008). From the periphery, nociceptive signals follow the ascending pathway to the superior centres of the brain (Marchand, 2008).

1.4.2 Ascending tracts

From the periphery to the spinal cold. When potentially harmful stimuli are detected by peripheral nociceptive fibres (Aδ and C fibres), these first order neurons will send afferent signals to the spinal cord through the dorsal root ganglion. The first order neurones will then synapse with the second order neurones in the dorsal horn of the spinal cord (Marchand, 2008).

From the spinal cord to the thalamus. From the second order neurons in the spinal cord, the afferent signals will decussate immediately and ascend to the thalamus, where they synapse with the third order neurones (Farmer & Aziz, 2014; Marchand, 2008; Steeds, 2009). Hence, the nociceptive signals project to the thalamus on the contralateral side of the nociceptive simulation (Marchand, 2008).

From the thalamus to the cortex. Located in the centre of the brain, the thalamus is an important relay in pain perception and the gateway to the cortex. Nociceptive signals ascend from the spinal cord to the thalamus through the spinothalamic or the spinoreticular tract (Marchand, 2008). The former projects signals to the lateral thalamus. From there, thalamocortical fibres will ascend information to the primary and secondary somatosensory cortices (Marchand, 2008). This pathway determines the sensory components of pain (e.g. location and duration of pain) (Farmer & Aziz, 2014; Marchand, 2008; Steeds, 2009). The spinoreticular track leads nociceptive information to the medial thalamus (Marchand, 2008). From there, third-order neurones will ascend the information to the anterior cingulate cortex (ACC) and the insula (please see **Figure 1**). These brain regions determine the affective components of pain (e.g. pain unpleasantness) (Farmer & Aziz, 2014; Marchand, 2008).

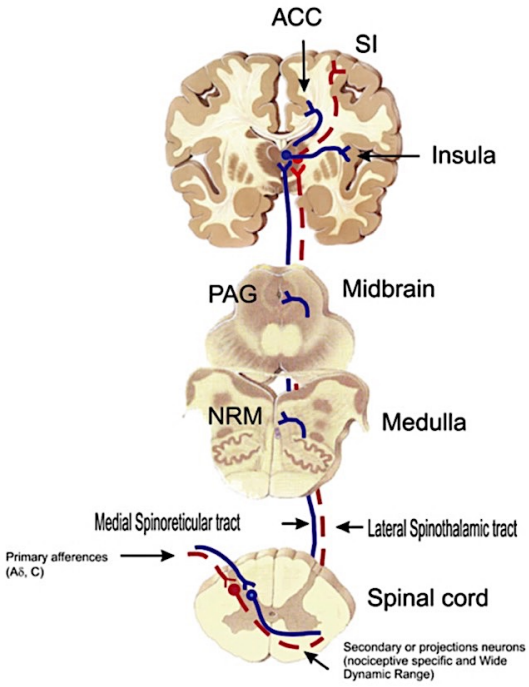

Figure 1. Ascending pain and pain modulation pathways

Extracted from Marchand (2008)

1.4.3 Sensory processing

The somatosensory cortex. Located posterior to the central sulcus, the somatosensory cortex is divided into the primary somatosensory cortex (SI) and the secondary somatosensory cortex (SII) (Marchand, 2008). The former receives projections from the ventral posterior lateral thalamus (Marchand, 2008). A review of positron emission tomography (PET) studies from Schnitzler & Ploner (2000) revealed that the repeated administration of heat stimuli to the dorsum of the hand and feet induce activations in the SI contralateral to the location stimulated and a somatotopic arrangement of pain in SI, suggesting that SI plays a role in the localization of pain (Schnitzler & Ploner, 2000). The medial part of the somatosensory cortex will receive information from rostral regions of the body such as the face or hands and the lateral regions of the cortex receive input from caudal regions such as the feet (J. C.W. Brooks, Zambreanu,

Godinez, Craig, & Tracey, 2005). Furthermore, a review showed that studies investigating the relationship between pain intensity and cerebral activations found a positive relationship between SI and pain intensity ($r=0.69$, $p<0.005$); however, pain unpleasantness did not correlate with SI activations (Coghill, Sang, Maisog, & Iadarola, 1999; Porro, Cettolo, Francescato, & Baraldi, 1998; Schnitzler & Ploner, 2000). Secondly, SII receives projections from the ventral posterior inferior thalamus and plays a role in tactile discrimination, which allows recognition of the type of stimulus (e.g. pressure or temperature), stimulus roughness or stimulus size (J. Brooks & Tracey, 2005; Schnitzler & Ploner, 2000). Taken together, both somatosensory cortices are involved in the sensory discrimination of pain; SI is involved in spatial discrimination and SII in tactile discrimination (Marchand, 2008).

Insula. The insula is located between the frontal and temporal lobe and can be subdivided into the posterior and the anterior insula (Petrovic, Petersson, Hansson, & Ingvar, 2002). While the posterior insula is involved in interoception (one's own perception of their bodily state), the anterior insula is involved in emotional awareness (Craig, 2009).

The posterior insula allows the processing of thermal and painful stimulation (Craig, 2009). A review by Garcia-Larrea (2012), focusing on the role of the posterior insula in pain paradigms, has reported that patients with lesions to the posterior insula, caused by a stroke, suffered loss of pain and temperature sensations. These findings were also reported in a review by J. Brooks & Tracey (2005). Furthermore, functional neuroimaging meta-analyses have shown that the posterior insula is also involved in the processing of stimulus intensity and location (J. Brooks & Tracey, 2005; K. B. Jensen et al., 2016; Wiech et al., 2010).

1.4.4 Emotional Processing

It has been proposed that three major brain regions are involved in the affective processing of pain; namely the anterior insula, the amygdala and the ACC (Fenton et al., 2015).

Anterior insula. The anterior part of the insula is a limbic structure mainly involved in emotional awareness (Lamm, Decety, & Singer, 2011). A review on the structure and function of the insula by Uddin, Nomi, Herbert-Seropian, Ghaziri, & Boucher (2017) has reported significant activations in the anterior insula in participants viewing images of emotional facial expressions (fear, disgust or happy), compared to neutral facial expressions. In addition, the anterior insula has also shown activations in individuals receiving a noxious stimulus (Fenton et al., 2015). Meta-analyses on functional brain imaging in response to pain have shown consistent activations of the anterior insula during continuous noxious heat stimulation (e.g. thermode) or noxious cold stimulation (e.g. cold water bath) in healthy volunteers (Farrell, Laird, & Egan, 2005; Peyron, Laurent, & Garcia-Larrea, 2000). Notably, experimental studies have shown that viewing pictures of negative emotional faces while concurrently receiving noxious stimulation causes even greater anterior insula activations (Dunckley et al., 2005; Phillips et al., 2003). Furthermore, greater activation in the anterior insula was revealed in participants who were asked to give an affective evaluation of pain, comparatively to participants not attending to pain unpleasantness (Jonathan C.W. Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002; Kong et al., 2006). Finally, a review on studies investigating lesions to the anterior insula has shown that individuals with lesions in this region have reduced pain affect responses to nociceptive stimuli (Schnitzler & Ploner, 2000). Taken together, these findings strongly support the hypothesis that the anterior insula is involved in the integration of emotional states and interoceptive states

(Craig, 2009; K. B. Jensen et al., 2016; Schnitzler & Ploner, 2000). Thus, the role of the anterior insula has often been linked to the emotional processing of the painful experience (Farrell et al., 2005; Fenton et al., 2015; Peyron et al., 2000).

Amygdala and ACC. Other regions such as the amygdala and the ACC have also shown involvement in the affective processing of pain, although results are not as robust as in the case of the anterior insular (Stevens, Hurley, & Taber, 2009). Firstly, the amygdala is an almond shaped structure located in the temporal lobe and forms part of the limbic system (Carrasquillo & Gereau IV, 2008). This structure is mainly known for its role in emotional processing, such as fear and stress (Carrasquillo & Gereau IV, 2008; Corder et al., 2019). Precisely, by integrating sensory information, the amygdala provides an emotional value to the sensory input, either positive (e.g. happy) or negative (e.g. fear). By using a similar protocol as Jonathan C.W. Brooks et al (2002) and Kong et al (2006) (shown above), Kulkarni et al (2005) observed significant increased activations in the amygdala when participants attended to pain unpleasantness. Thus, the activation of the amygdala during nociceptive stimulation has been linked to the emotional processing of pain.

Lastly, the ACC, wrapped around the corpus collosum, can be subdivided into two; the dorsal ACC and the ventral ACC (Stevens et al., 2009). The ventral ACC, also known as the pregenual ACC, is implicated in the integration of the autonomic system and in the emotional processing of stimuli (Stevens, Hurley, & Taber, 2011; Sturm et al., 2013). In the context of pain, the ventral ACC has been linked to the affective processing of pain (e.g. pain unpleasantness, fear and stress) (Tracey & Mantyh, 2007; Wiech & Tracey, 2009). Indeed, increased pain unpleasantness is correlated with increased activity in the ventral ACC (L.

Becerra, Navratilova, Porreca, & Borsook, 2013; Kulkarni et al., 2005). The dorsal ACC is involved in cognitive control and will be further development in the following section.

In brief, activations in the amygdala and in the ventral ACC has been reported in studies investigating the affective component of pain. However, these findings are not consistent throughout all studies, implying that their role in pain perception may not be fully understood to date.

1.4.5 Cognitive processing

As mentioned earlier, several cognitive processes, such as pain anticipation and placebo analgesia, have an important influence on pain perception (Wiech et al., 2008). Empirically speaking, the prefrontal cortex, the dorsal ACC and the middle cingulate cortex (MCC) are the three brain regions that have the most consistently shown increased activity during cognitive processing (Stevens et al., 2009).

The dorsolateral prefrontal cortex. The prefrontal cortex is essential for decision-making, planning and plays a pivotal role in the cognitive processing of pain (Euston, Gruber, & McNaughton, 2012). In a functional magnetic resonance imaging (fMRI) study on placebo analgesia, subjects participated in two experiments, a first experiment applying shock pain and a second experimental applying thermal pain (Wager et al., 2004). In each experiment, subjects participated in a control trial, where they were told a lotion offered no relief, and in a placebo trial, where they were told a lotion would offer pain relief. Results of this study showed increased activity in the dorsal lateral prefrontal cortex (DLPFC) during pain relief anticipation, compared to the control trial. Moreover, this increase in activation was significantly correlated

with the magnitude of the reduction in reported pain between the control and the placebo trial. These correlations were found in both the shock study ($r=0.62$, $p<0.005$); and the thermal study ($r=0.60$, $p<0.005$) (Wager et al., 2004). Coherently, increased activity in the DLPFC during placebo analgesia and pain anticipation was also reported in two reviews (Tracey & Mantyh, 2007; Wiech et al., 2008).

Cingulate cortex. The cingulate cortex is thought to contain several specialized subregions which may hold unique functions (Vogt, 2016). The ACC was first discussed in the section above, however the role of the cingulate cortex may be further expanded.

The MCC shares connectivity with the prefrontal cortex and is involved in cognitive functions such as decision-making and cognitive control, and some authors have hypothesized that the MCC plays a key role in cognitive pain modulation (Stevens et al., 2011). In order to identify brain regions implicated in pain anticipation, functional neuroimaging studies performed analyses comparing groups receiving a pre-stimulation cue indicating the level of pain of the stimulus, with a group receiving no pre-stimulation cue (Wiech et al., 2010). Both groups received the same nociceptive stimulus. Results showed increased activity in the MCC when the stimulus was anticipated to be painful. Furthermore, stronger MCC activations also correlated with stronger pain perception (Wiech et al., 2010). Importantly, several meta-analyses have shown activation in the MCC following nociceptive stimulation and following attention and anticipation of pain (Porro, Cettolo, Francescato, & Baraldi, 2003; Wiech et al., 2010). These results indicate the implication of the MCC in the cognitive processing of pain.

The dorsal ACC is adjacent to the MCC (Stevens et al., 2009). Based on the well-known involvement of the dorsal ACC in cognitive control (e.g. ability to flexibly adjust behaviour)

and decision making, some authors have hypothesized that the dorsal ACC may play a key role the cognitive processing of pain (e.g. attention to pain) (Shenhav, Cohen, & Botvinick, 2016; Tracey & Mantyh, 2007; Wiech & Tracey, 2009). Yet, results of fMRI research have been inconsistent thus far, and additional research is needed to fully understand the role of the dorsal ACC in pain modulation.

1.5 Endogenous pain modulation system

Pain perception is a dynamic phenomenon that involves the modulation of nociceptive signals at multiple levels of the CNS (Marchand, 2008). These endogenous pain modulation systems involve either excitatory (increasing the nociceptive response) or inhibitory (inducing analgesia) mechanisms.

1.5.1 The excitatory mechanisms

Central sensitization in the spinal cord. Central sensitization is characterized by an augmented response to nociceptive stimuli (hyperalgesia) or a pain response to non-nociceptive stimuli (allodynia) (Marchand, 2008). At the mechanistic level, a high frequency stimulation of C fibres at the same intensity will trigger a progressive increase of action potential discharge in the spinal cord (Marchand, 2008). The prolonged firing of C fibres will allow the release of glutamate, which will in turn bind to N-methyl-D-aspartate (NMDA) receptors, found in the spinal cord, and will induce spinal sensitization. In humans, this reaction evokes an increase in sensitivity to noxious stimuli (Bennett, 2000; Marchand, 2008; Potvin, Grignon, & Marchand, 2009). In experimental settings, two distinct psychophysical paradigms are used to study central

sensitization, namely temporal summation and spatial summation (Marchand & Arsenault, 2002).

Temporal and spatial summation. Temporal summation is defined as repeated stimulation to the same surface area at the same intensity for a prolonged time. The high frequency of painful stimulation causes a temporal stimulation of the C fibres due to their slow conduction rate, resulting in increased pain perception (pain intensity and pain unpleasantness) (Marchand, 2008). Spatial summation, on the other hand, can be defined as the effect of the size of the surface area stimulated on pain perception (pain intensity, pain unpleasantness and pain threshold) (Marchand & Arsenault, 2002). A larger stimulated area will increase the number of nociceptors recruited, resulting in increased pain perception (Marchand, 2008). However, prolonged spatial stimulation may eventually cause pain inhibition (Marchand & Arsenault, 2002). Consequently, spatial summation paradigms may also be used to study pain inhibitory mechanisms.

1.5.2 Inhibitory mechanisms

The inhibitory conditioned pain modulation system. The inhibitory conditioned pain modulation (ICPM) theory suggests that a localized painful stimulation will cause inhibition of spinal neurons, which in turn will produce diffused analgesia (pain inhibition over the whole body) (Marchand 2008). According to this theory, diffused analgesia will occur when an intense nociceptive stimulus is administered for a prolonged time on a large surface area (e.g. the forearm). This in turn will cause reduced pain perception, a phenomenon known as *pain inhibits pain* (Potvin et al., 2009). When testing ICPM in healthy subjects, the results generally show an

hypoalgesic effect (Marchand, 2008; Potvin et al., 2009). However, this phenomenon appears to be absent or reduced in many chronic pain patients (Edwards, Ness, Weigent, & Fillingim, 2003; Staud, Robinson, Vierck Jr, & Price, 2003).

The descending pathway. The mechanisms underlying the ICPM phenomenon involve descending pathways at the brainstem level (Marchand, 2008). These mechanisms start a cascade of reactions beginning with the recruitment of endogenous opioids in the periaqueductal grey (PAG) (Steeds, 2009). The PAG is a brainstem structure, located precisely in the midbrain, containing both opioid and cannabinoid receptors (Behbehani, 1995; Steeds, 2009). The stimulation of these receptors will then activate cells in the nucleus raphe magnus (NRM) (Steeds, 2009). The latter is located in the rostral ventral medulla (RVM). When the cells in the NRM are activated, they cause a release of serotonin in the spinal cord, which in turn blocks the transmission of pain signals, causing diffuse analgesia and blocking both hyperalgesia and allodynia effects (Ossipov, Morimura, & Porreca, 2014; Pud, Granovsky, & Yarnitsky, 2009a; Steeds, 2009).

Located in the pons, the locus coeruleus also plays a role in pain inhibition and is comprised of a large population neurones producing noradrenaline (Llorca-Torralba, Borges, Neto, Mico, & Berrocoso, 2016; Ossipov et al., 2014). The locus coeruleus receives inputs from the PAG and the RVM and projects noradrenaline into the spinal cord, causing the suppression of nociceptive signals (Muta, Sakai, Sakamoto, & SUzuki, 2012; Ossipov et al., 2014; Schwarz & Luo, 2015).

In brief, the PAG, the NRM and the locus coeruleus are engaged in the ICPM phenomenon. Their activation leads to the release of neurotransmitters including opioids,

cannabinoids, serotonin and noradrenaline that induce diffuse analgesia. This diffuse analgesia observed during the ICPM phenomenon can be shown during experimental procedures.

Experimentally inducing ICPM. In experimental settings, ICPM can be measured using two stimuli that induce pain; a test stimulus and a conditioning stimulus (Marchand & Arsenault, 2002). The most commonly used test stimulus and conditioning stimulus are respectively a contact thermode generating heat and the cold pressor test (CPT) (consisting of a cold-water bath) (Pud et al., 2009a). The CPT has been preferred over other stimuli as it involves both temporal and spatial summation (immersion of the whole arm into a water bath) (Marchand & Arsenault, 2002). Indeed, there are three main factors allowing the activation of ICPM: spatial summation, temporal summation, and the intensity of the conditioning stimulus (the stronger the conditioning stimulus, the stronger the analgesia measured will be) (Marchand & Arsenault, 2002). During the experimental procedure, the pain response to the test stimulus was measured twice, each time on a different surface of the skin to avoid peripheral sensitization. The experimental temperature is individually adapted. Although the experimental temperature used for both administrations is the same, participants typically report decreased pain perception during the second test stimulus, suggesting that endogenous pain inhibition mechanisms have been recruited (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016a; Pud et al., 2009a).

Importantly, ICPM can be measured through two different paradigms: the sequential paradigm and the parallel paradigm (Kennedy et al., 2016a). During the sequential paradigm, the test stimulus is measured once before the conditioning stimulus and once after the conditioning stimulus. As for the parallel paradigm, the test stimulus is measured firstly before the conditioning stimulus and secondly at the same time as the application of the conditioning

stimulus (Kennedy et al., 2016a). With the parallel paradigm, there is a possibility that the conditioning stimulus is acting as a distraction stimulus because it is applied concomitantly with the test stimulus (Kennedy et al., 2016a). Therefore, it is still unclear if the parallel paradigm truly measures the effect of pain modulation or of pain distraction. As mentioned earlier, distraction of a painful experience leads to a decrease in pain perception. For this reason, many have opted to use the sequential paradigm (Kennedy et al., 2016a). However, an important problem may also arise when using the sequential paradigm that has not been discussed in the literature until recently. Precisely, some articles have shown that the interruption of pain causes an increase in pleasure induced by pain relief (Leknes et al., 2008; Leknes & Tracey, 2008). Consequently, it is uncertain if the sequential paradigm is truly measuring ICPM (e.g. *pain inhibits pain* phenomenon), or if the sequential paradigm is measuring pain inhibition caused by pleasant pain relief.

1.6 Pleasant pain relief

Over the last decade, several experimental studies have shown that pain can be downregulated by positive emotional states induced by rewarding stimuli such as emotionally positive pictures, pleasant odours and pleasurable music (Kut et al., 2011; Leknes & Tracey, 2008). Pleasure induced hypoalgesia has been defined as reduced pain perception when concurrently receiving a pleasant and a nociceptive stimulus (Navratilova & Porreca, 2014). In a fMRI study, participants received noxious heat stimulation with a thermode while concurrently looking at images of their romantic partner (Younger, Aron, Parke, Chatterjee, & Mackey, 2010a). This research found significant decreases in key regions of the pain matrix (e.g. thalamus and posterior insula) in participants looking at images of their partner in comparison

to those who did not view pictures on their loved ones (Younger et al., 2010a). In a similar study conducted on 22 healthy individuals, participants viewing pleasant emotional pictures *before* receiving noxious heat stimulation from a thermode had increased pain tolerance compared to the control group, suggesting a potential role of reward-analgesia in pain modulation (Kut et al., 2011). Reward analgesia has also been tested in animals. When conducting experiments on reward-analgesia on rats, pain perception is measured as the time taken to withdraw from a painful stimulus. In fact, studies conducted on male and female Sprague-Dawley rats receiving noxious heat on their hind paw during voluntary drinking observed a significant increase in the time taken to remove their paw from the noxious surface when rats where receiving a sucrose solution as compared to solely water (Davies et al., 2019; Ren, Blass, Zhou, & Dubner, 1997). Notably, to further understand the reward system, these studies have also investigated its associated neurobiology.

More specifically, the reward paradigm induces pain-relieving effects primarily through dopamine, a catecholamine neurotransmitter (Potvin et al., 2009). The midbrain dopamine neurons exert their modulatory role through the mesocorticolimbic pathway, composed mainly of limbic, striatal and pre-frontal brain structures (Lidstone, de la Fuente-Fernandez, & Stoessl, 2005). External cues, such as pleasant stimuli, rewarding drugs or reward-predicting stimuli (e.g. placebo analgesia) can induce positive states in humans causing stimulation of the mesolimbic reward pathway. Once stimulated, dopamine neurons, which project from the ventral tegmental area to the nucleus accumbens (e.g. ventral striatum), the amygdala and the orbital frontal cortex, cause decreased pain (Altier & Stewart, 1999; Lidstone et al., 2005; Navratilova, Atcherley, & Porreca, 2015). In addition, a review has highlighted that there is a positive relationship between the amount of pain reduction (caused by pleasant stimuli) and

increased activation in the ventral striatum (reward region) (Navratilova & Porreca, 2014). Taken together, these results show the existence of a relationship between pain and pleasure.

Pain and pleasure are two states that appear to fall on opposite sides of a hedonic continuum (pleasant or unpleasant sensations) (Leknes et al., 2008). According to the opponent process theory, when a negative stimulus, such as noxious heat, is abruptly terminated, a feeling of the opposite hedonic state will be felt (e.g. pleasure) (Leknes et al., 2008). In theory, it has been proposed that pain relief may induce a pleasant feeling (Ellingsen et al., 2013; Leknes et al., 2008). To test this model, a psychophysical study induced noxious thermal heat pain using a thermode in healthy participants and found a significant positive correlation between pain intensity and pain relief ($r=0.82$, $p=0.012$), suggesting that the greater the intensity of the noxious stimulus, the greater the intensity of the relief will be (Leknes et al., 2008). The intensity of the noxious stimulus is individually determined and must reach a minimum pain rating of 50/100 (0 no pain- 100 most intense pain imaginable) in order for relief from pain to be measured (Leknes et al., 2008). Finally, the higher the value of a pleasant stimulus the more this stimulus will able to reinstate our bodies homeostasis (bodily equilibrium) (Leknes et al., 2008). Equally, similar findings have been observed in fMRI studies.

Neuroimaging studies have investigated cerebral activations during pain onset/offset (or pleasant pain relief) (L. Becerra et al., 2013; Lino Becerra & Borsook, 2008; Sprenger, Bingel, & Büchel, 2011). These studies have generally used thermal noxious pain induced with a thermode while participants lie supine in a functional scan. During pain onset, the studies showed increased activations in pain-related regions such as the insula, SI and SII but one research team found decreased activations in the nucleus accumbens (L. Becerra et al., 2013; Lino Becerra & Borsook, 2008; Sprenger et al., 2011). However, these results regarding the

nucleus accumbens should be taken prudently as other research have failed to show a deactivation in the nucleus accumbens (K. B. Jensen et al., 2016; La Cesa et al., 2014). The role of the nucleus accumbens may therefore be more complex and need further research. Contrariwise, during pain offset, studies noted decreased activation in the insula and increased activations in the nucleus accumbens and the orbital frontal cortex, which are regions shown to encode positive hedonic states (Lino Becerra & Borsook, 2008; Leknes et al., 2012). Relief from pain can therefore be viewed as pleasurable and may even contain rewarding benefits (L. Becerra et al., 2013; Leknes, Lee, Berna, Andersson, & Tracey, 2011; Younger et al., 2010a).

It is noteworthy that the fMRI studies mentioned until now have used similar stimuli to induce pain and measure brain activations during a painful stimulation, that is, thermal noxious stimulation using a thermode. We have previously mentioned that pleasant pain relief increases with greater pain intensity (Marchand & Arsenault, 2002). That being said, the CPT may be better suited to measure pleasant pain relief, as it is composed of both spatial and temporal characteristics. In fact, studies using the CPT to induce pain on healthy individuals have found significant activations in the thalamus and the insula (La Cesa et al., 2014; Lapotka, Ruz, Ballesteros, & Hernández, 2016). Moreover, the CPT has been used as a conditioning stimulus in the sequential paradigm in studies investigating the ICPM phenomenon (Kennedy et al., 2016a; Marchand & Arsenault, 2002; Pud et al., 2009a). However, to our knowledge, none of these studies have precisely looked at pleasant pain relief induced by the CPT or at the possible relationship between ICPM and pleasant pain relief.

In this sense, our limited knowledge on the pleasant pain relief phenomenon raises a methodological problem when using the sequential paradigm to measure ICPM. In the sequential paradigm, the test stimulus is measured once before and once after the conditioning

stimulus (Kennedy et al., 2016a). In healthy individuals, studies have observed reduced pain perception between the two test stimulus (Potvin & Marchand, 2016a; Tousignant-Laflamme, Pagé, Goffaux, & Marchand, 2008). However, this pain reduction may be due to pleasant pain relief, meaning that the sequential paradigm may be measuring pain reduction induced by pleasant pain relief, rather than the ICPM phenomenon.

1.7 Objectives

Psychological investigations have suggested that relief from aversive stimuli can be perceived as pleasurable (Navratilova & Porreca, 2014). Even with the growing interest in this field, several aspects still remain understudied. Precisely, studies have used thermodes to induce pain and thus measure pleasant pain relief. However, the CPT may be better suited than the thermode because of its ability to induce greater pain and as a result causing greater pleasant pain relief. Consequently, the main objective of this memoir was to further our understanding on pleasant pain relief. In order to do so, two separate studies have been conducted. The first study sought out to investigate the possible relationship between pleasant pain relief, ICPM and subclinical psychological symptoms. This psychophysical article was published, and the corresponding article is found in the following section. In a second study, we conducted both psychophysical and fMRI testing with the objective of investigating the relationship between pleasant pain relief and brain activations and de-activations during pain onset. This study will be explained in detail in chapter 3 of this memoir.

Study 1. This study is a psychophysical study testing the relationships between ICPM, the pleasant pain relief phenomenon and subclinical psychological symptoms. Investigating the

relationship between ICPM and pleasant pain relief by using the sequential paradigm will allow us to determine if the reduction in pain perception between the first and second administration of the test stimulus is confounded by the pleasant pain relief phenomenon. We evaluated this relationship by inducing ICPM using a thermode (test stimulus) and the CPT (conditioning stimulus) and by measuring pleasant pain relief using the CPT. Moreover, to our knowledge, the relationship between pleasant pain relief and negative emotional states still remains largely unstudied in this field. For this reason, the second objective of this paper was to evaluate the possible relationship between pleasant pain relief and anxio-depressive subclinical symptoms.

We hypothesized that there may be a positive relationship between ICPM and pleasant pain relief and a negative relationship between anxio-depressive subclinical symptoms and pleasant pain relief.

For this study, my contributions were the following; clinical testing of all participants, data analysis and writing the article shown in the following section.

Study 2. Studies investigating brain activations and de-activations during pain onset and pain offset have observed opposite results, that is, **increased activations in pain-related regions** during pain onset and **decreased activations in pain-related regions** and **increased activations in reward regions** during pain offset (L. Becerra et al., 2013; Lino Becerra & Borsook, 2008; Sprenger et al., 2011). Similarly, in this fMRI study, we sought to further extend the first study by, firstly, observing all cerebral activations/deactivation during pain onset. More specifically, past researches have failed to consistently show deactivation in reward regions when using a thermode to induce noxious pain. In our research, we opted to use the CPT to determine if this stimulus would be better suited to observe such deactivations in brain reward

regions during pain onset. Secondly, we sought to investigate all possible relationships between brain activations and de-activations during pain onset with pain perception, pleasant pain relief and subclinical psychological symptoms. In order to do so, noxious pain was induced to participants during fMRI scanning with a modified CPT. This modified CPT consisted of frozen gel that was placed on participants' right foot.

We hypothesized that the modified CPT would induce activations in pain related regions and deactivations in reward regions during its administration.

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Pleasant Pain Relief and Inhibitory Conditioned Pain Modulation: A Psychophysical Study

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Abstract

Background Inhibitory conditioned pain modulation (ICPM) is one of the principal endogenous pain inhibition mechanisms and is triggered by strong nociceptive stimuli. Recently, it has been shown that feelings of pleasantness are experienced after the interruption of noxious stimuli. Given that pleasant stimuli have analgesic effects, it is therefore possible that the ICPM effect is explained by the confounding effect of pleasant pain relief. The current study sought to verify this assumption. ***Methods*** Twenty-seven healthy volunteers were recruited. Thermal pain thresholds were measured using a Peltier Thermode. ICPM was then measured by administering a tonic thermal stimulus before and after a cold-pressor test (CPT). Following the re-administration of the CPT, pleasant pain relief was measured for 4 minutes. According to the opponent process theory, pleasant relief should be elicited following the interruption of a noxious stimulus. ***Results*** The interruption of the CPT induced a *mean* and *peak* pleasant pain relief of almost 40% and 70%, respectively. Pleasant pain relief did not correlate with ICPM amplitude, but was positively correlated with pain level during the CPT. Finally, a negative correlation was observed between pleasant pain relief and anxiety. ***Discussion*** Results show that the cessation of a strong nociceptive stimulus elicits potent pleasant pain relief. The lack of correlation between ICPM and pleasant pain relief suggests that the ICPM effect, as measured by sequential paradigms, is unlikely to be fully explained by a pleasant pain relief phenomenon.

Key words

Pain modulation; pleasant pain relief; anxiety

1. Introduction

Chronic pain affects approximately 22% of the adult population (Tamburin, Paolucci, Smania, & Sandrini, 2017), and is a complex phenomenon resulting from biological, psychological and social factors. Among these factors, the importance of central mechanisms, such as the activity of endogenous pain excitatory and inhibitory systems, are increasingly acknowledged (DeSantana & Sluka, 2012; Kwon, Altin, Duenas, & Alev, 2014; Tousignant-Laflamme et al., 2008). Indeed, growing evidence suggests that endogenous pain modulation mechanisms are impaired in nearly every type of chronic pain disorders, and that alterations are particularly significant in neuropathic and functional pain syndromes (Lewis, Heales, Rice, Rome, & McNair, 2012; Clifford J. Woolf, 2011; Yarnitsky, 2015).

Inhibitory conditioned pain modulation (ICPM) is one of the principal endogenous pain inhibition mechanisms (Lewis, Rice, & McNair, 2012a; Moont, Crispel, Lev, Pud, & Yarnitsky, 2011; Nahman-Averbuch et al., 2013). The ICPM theory postulates that a nociceptive stimulation will reduce another nociceptive stimulation if it occurs on a body surface distant from the pain surface (Le Bars, Dickenson, & Besson, 1979a, 1979b). Pre-clinical studies have shown that the ICPM effect is mediated by brain stem and bulbo-spinal mechanisms (Basbaum & Fields, 1978; Marchand, 2008; Millan, 2002; Willer, Bouhassira, & Le Bars, 1999). When triggered, ICPM causes a diffuse diminution of pain throughout the body.

From an experimental point of view, two types of paradigms are used to measure ICPM: in the *parallel* ICPM paradigm, a noxious stimulus (test stimulus) is applied before and at the same time as a heterotopic conditioning painful stimulus, while in the *sequential* paradigm, the test stimulus is applied before and after a heterotopic conditioning painful stimulus (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016b). Considering that it is unclear if the *parallel* ICPM

paradigm truly measures the ICPM effect or a distracting effect, some investigators prefer the *sequential* paradigm which removes the potential effect of distraction (Olesen, Van Goor, Bouwense, Wilder-Smith, & Drewes, 2012; Valencia et al., 2014; Valencia, Kindler, Fillingim, & George, 2012). It is indeed well known that pain experience is reduced when individuals are engaged in cognitive tasks (e.g. arithmetic, working memory, etc.) (Moont et al., 2011). This raises the possibility that the conditioning stimulus actually distracts participants from their pain when it is concomitantly administered at the same time as the test stimulus. Conversely, some laboratories have made mention of their preference of the *parallel* ICPM paradigm over the *sequential* one, considering that ICPM effect gradually fades over time and that the precise duration of this effect remains uncertain (Pud, Granovsky, & Yarnitsky, 2009b).

Another potential limitation of *sequential* ICPM paradigms that has gone unnoticed is that the pain reduction observed using these paradigms may be confounded by the pleasant pain relief phenomenon. According to the opponent process theory, when a stimulus causing deviation from homeostasis is terminated, the opposite sensation will be felt (Andreatta, Mühlberger, & Pauli, 2016). Consistently with this theory, recent research has shown that the interruption of a noxious stimulus causes a feeling of pleasantness (Leknes et al., 2008), similar to the feeling often observed in reaction to analgesic drugs (Leknes et al., 2008). Given that pleasant stimuli (e.g. music, odors, attractive faces, etc.) are well-known for producing analgesic effects (Dobek, Beynon, Bosma, & Stroman, 2014; Prescott & Wilkie, 2007; Younger, Aron, Parke, Chatterjee, & Mackey, 2010b), it is therefore possible that the interruption of the conditioning stimulus elicits a pleasant feeling, which decreases in turn pain perception when the second test stimulus is re-applied. If so, the reduction in pain perception observed during the

second test stimulus would not reflect a pure ICPM effect but rather a pleasure-induced analgesia effect, at least partially.

In the past, our research team has pursued several studies on ICPM using a sequential paradigm, consisting in the application of a tonic noxious heat stimulation to the left forearm of participants eliciting moderate pain, administered before and after the immersion of their right arm in a bath of cold water. This paradigm has allowed us, among others, to show that pain perception is reduced during the second application of the test stimulus, relative to the first one, indicating that endogenous pain inhibition mechanisms have been recruited (Normand et al., 2011; Potvin & Marchand, 2016b). In the current study, we sought to examine a hypothetical association between ICPM and pleasant pain relief, using our validated ICPM procedure (Tousignant-Laflamme et al., 2008). Thus far, most studies on pleasant pain relief have used heating thermodes to elicit the phenomenon (Leknes et al., 2008; Mohr et al., 2009). The current study differed in that we measured pleasant pain relief after the interruption of the cold-pressor test, given that it is the conditioning stimulus used in our *sequential* paradigm to trigger the ICPM effect. The secondary objective of the current study was to examine the potential associations between pleasant pain relief and anxio-depressive sub-clinical symptoms. Although several experimental studies have shown that anxiety and depression influence pain perception in experimental settings (De Heer et al., 2014; Defrin, Schreiber, & Ginzburg, 2015; Zambito Marsala et al., 2015), the influence of these variables on pleasant pain relief is unknown.

2. Method

2.1 Participants

We recruited a total of 27 (14 women) healthy participants, aged between 18 and 35 years old (mean age 25.1 years ± 4.27, mean; standard error of the mean (SEM)) (Table 1). Exclusion criteria were the following: (1) any DSM-V Axis psychiatric disorder (including substance use disorders); (2) centrally-acting medications; (3) neurologic disorders; and (4) any unstable medical condition. In particular, none of the participants suffered from chronic pain and none had significant acute painful symptoms as determined with the *Brief Pain Inventory* (mean pain= 0.9 ±0.4) (Atkinson et al., 2010; Poundja, Fikretoglu, Guay, & Brunet, 2007). Sub-clinical psychological symptoms (e.g. depression, anxiety, anhedonia and pain) were evaluated, respectively, with the French versions of the *Beck Depression Inventory-II* (BDI-II) (Lahlou-Laforêt, Ledru, Niarra, & Consoli, 2015), the *State and Trait Anxiety Inventory*-state subscale (STAI-S) (Barnes, Harp, & Jung, 2002; Gauthier & Bouchard, 1993) and the *Snaith-Hamilton Pleasure Scale* (SHPS) (Ameli et al., 2014; Loas et al., 1997). Recruitment was made via word of mouth and through online advertisement (Kijiji). Each participant signed a detailed consent form, and the local ethics committee approved the research.

2.2 Inhibitory conditioned pain modulation (ICPM) paradigm

2.2.1 Heat pain threshold and tolerance. Thermal pain threshold and tolerance were measured by applying a 3 cm^2 Peltier thermode on the left forearm of participants (TSA II, Medoc, Advanced Medical Systems, Ramat Yishai, Israel) (Potvin & Marchand, 2016b).This heating plate was connected to a computer and allowed a precise control of temperatures. Experimental temperatures were initially set at 32°C and gradually increased at a rate of 0.3°C per second. To

ensure that there would be no peripheral sensitization, the thermode was moved to a different area of the forearm for every test. Participants were asked to report the moment at which sensation changed from heat to pain (thermal pain threshold, VAS=1) (Leknes et al., 2008; Potvin & Marchand, 2016b) and the moment the sensation of pain was at its highest (most intense pain tolerable) (thermal pain tolerance, VAS=100). For each participant, the temperature inducing moderate pain (T50) was also measured. Upon the first application, these measures were taken verbally to ensure the participant's comprehension of the procedure. During the second and third application, these measures were reported by participants using a computerized visual analog scale (VAS). This scale ranged from 0 (no pain) to 100 (most intense pain tolerable) (Potvin & Marchand, 2016b).

2.2.2 Tonic heat pain perception. The *test stimulus* consisted of a continuous heat stimulation that induced moderate pain (T50) for 2 minutes (Potvin & Marchand, 2016b). This heat stimulation was administered with a thermode on the left forearm of participants. The temperature of the thermode quickly reached T50, an individually predetermined temperature (baseline at 32°C and increase rate of 0.3°C per second) and then remained constant for the remaining time. However, participants were not told that the temperature was kept constant (Potvin et al., 2008). During the administration of the test stimulus, individuals were instructed to measure pain intensity using the same COVAS as previously mentioned. The test stimulus was administered twice, separated by the administration of the cold pressor test (CPT) (e.g. the conditioning stimulus).

2.2.3 Conditioning stimulus. The CPT consisted of the immersion of the opposite arm (right arm) into a bath of ice water that was kept constant at 10°C, for a maximum of 2 minutes, by continuously recirculating the water (Julabo F33-HL Heating/refrigerated circulator). The temperature was chosen to be painful enough to elicit the endogenous analgesia effect yet tolerable for 2 minutes (Potvin & Marchand, 2016b). During the administration of the conditioning stimulus, participants were instructed to verbally report pain intensity and pain unpleasantness on a scale of 0 to 100. In order to differentiate between pain intensity and pain unpleasantness, two scenarios were presented to the participants. For pain intensity, they were asked to imagine themselves at their favourite concert; the music is extremely loud, and it damages their eardrums. In that scenario, the intensity is very high; however, it is not unpleasant because they enjoy the music. On the other hand, for pain unpleasantness, they were asked to imagine themselves studying the day before a final exam with loud construction noise outside their house. In that second scenario, the intensity of the noise is not high; however, it is extremely unpleasant. The measures for pain intensity and pain unpleasantness were taken at the moment the arm was immersed into the bath of cold water and afterwards every 30 seconds, until 120 seconds. With these measures, the mean pain intensity and mean pain unpleasantness were calculated for each participant. By measuring pain perception (using the test stimulus) before and after the conditioning stimulus, it was possible to measure ICPM. In other words, ICPM is defined as the reduction in pain perception observed between both administrations of the test stimulus (before and after the conditioning stimulus) (Valencia et al., 2014).

2.2.4 Pleasant pain relief. Pleasant pain relief was measured immediately after the conditioning stimulus. In order to explain to participants the pleasant pain relief phenomenon, we provided

an example similar to the one used by Lekness et al. (Leknes et al., 2008). Participants were asked to imagine themselves walking in a -30°C snowstorm for 20 minutes and finally arriving home to feel the warmth of the air inside the house. This warmth would induce the feeling of both pain relief and of pleasure (Leknes et al., 2008). Considering that the ICPM effect lasts for a short time span (approximately 10 minutes), it was important that the administration of the second test stimulus quickly follow the conditioning stimulus (Lewis, Heales, et al., 2012). Consequently, following the conditioning stimulus, the measure of pleasant pain relief was only taken once in order to avoid delaying the administration of the second test stimulus. The second test stimulus was then administered immediately after the score of pleasant pain relief was taken. To fully capture the dynamics of pleasant pain relief, thirty minutes after the full administration of the *sequential* ICPM paradigm, we re-administered the conditioning stimulus for 2 minutes. During the second administration of the conditioning stimulus, participants were again instructed to verbally report pain intensity and pain unpleasantness using the same scale as mentioned earlier (see section 2.2.3). Pleasant pain relief was measured immediately after the end of the immersion, and every 30 seconds afterwards for 4 minutes. To assess the pleasant pain relief, participants were asked to rate their level of pleasant pain relief on a scale of 0 ("I feel relief, but no pleasure") to 100 ("I feel relief and the most intense pleasure possible"). These ratings were used to calculate the mean and peak (the highest score) pleasant pain relief of each participant.

3. Statistical analyses

Two paired-sample t-tests were conducted. Firstly, we compared pain ratings of the test stimulus before and after the conditioning stimulus, as an index of ICPM efficacy. Secondly,

we compared two pleasant pain relief scores, measured after the separate administrations of the conditioning stimulus. To determine the relationship between the conditioning stimulus, ICPM, pleasant pain relief and subclinical symptoms, Pearson's correlation analyses were performed. We examined potential correlations: (i) between pain intensity and pain unpleasantness during the conditioning stimulus and pleasant pain relief (mean and peak); (ii) between ICPM efficacy and pleasant pain relief (mean and peak); (iii) between pain intensity and unpleasantness during the conditioning stimulus and ICPM efficacy; (iv), between psychological symptoms (STAI-S, BDI-II and SHPS) and pleasant pain relief (mean and peak) and finally (v) between psychological symptoms (STAI-S, BDI-II and SHPS) and pain (intensity and unpleasantness). The interclass correlation coefficient (ICC) estimate along with the 95% confidence intervals (CI) were calculated for mean pain intensity scores taken during each conditioning stimulus, mean pain unpleasantness scores taken during each conditioning stimulus, as well as for pleasant pain relief (first pleasant pain relief score taken immediately after each conditioning stimulus). ICC was calculated using a one-way random effect model and single measures were reported (Koo & Li, 2016a). This allowed us to determine the test-retest reliability of pain intensity and unpleasantness during both administrations of the conditioning stimulus and of both measures of pleasant pain relief. Values of ICC that are less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 are indicative of moderate reliability, and finally, values between 0.75 and 0.90 are indicative of excellent reliability (Koo & Li, 2016a). All variables had a normal distribution, as determined with the Shapiro-Wilks test for normality. All results are presented as mean ± standard error of the mean (SEM) and are considered significant at $p<0.05$. All analyses were performed using SPSS, version 24.

4. Results

4.1 Inhibitory conditioned pain modulation paradigm

4.1.1 Heat pain threshold and tolerance. During the pre-test, the thermal pain threshold of participants was 42.3°C ±0.7, the thermal pain tolerance was 47.2°C ±0.5, and the T50 was 45.9°C ±0.4.

4.1.1 Tonic pain perception. The mean pain ratings for the test stimulus administered before the conditioning stimulus was 67.4 ±3.3 and was reduced to 51.2 ±4.7 after the conditioning stimulus (mean difference= 16.1 ±3.0) (Figure 1). The difference between these pain ratings was significant ($t(26)=5.4$; $p<0.001$). During the conditioning stimulus, the mean pain intensity and mean pain unpleasantness were respectively 50.9 ±3.0 and 51.1 ±4.0.

4.1.2 Pleasant pain relief. During the second administration of the conditioning stimulus (30 minutes later), the mean pain intensity and mean pain unpleasantness were respectively 47.8 ±3.4 and 47.9 ±4.0. After this conditioning stimulus, pleasant pain relief measures were taken every 30 seconds for 4 minutes. The mean pleasant pain relief was 40.0 ±3.8 (Figure 2) and the *peak* pleasant pain relief was 69.3 ±4.4. Noteworthy, pleasant pain relief was also measured after the first administration of the conditioning stimulus. No significant difference was found between the two measures ($t(26)=0.81$; $p=0.936$).

4.2 Correlations of pleasant pain relief with other psychophysical measures

A significant correlation was observed between *mean* pleasant pain relief and pain intensity during the conditioning stimulus ($r=0.479$; $p=0.011$) (Figure 3). Likewise, a significant

correlation was also found between *peak* pleasant pain relief and pain unpleasantness during the conditioning stimulus (r=0.644; p<0.001) (Figure 4). Conversely, no significant correlations were found between pleasant pain relief (measured after the first conditioning stimulus) and ICPM efficacy (r=0.113; p=0.576), as well as between *mean* and *peak* pleasant pain relief (measured after the second conditioning stimulus) and ICPM efficacy (respectively, r=0.144; p=0.47, r=0.090; p=0.656). Finally, no significant correlations were found between pain intensity during the conditioning stimulus and ICPM efficacy (r=0.107; p=0.601), as well as between pain unpleasantness during the conditioning stimulus and ICPM efficacy (r=0.126; p=0.532).

4.3 Correlations of pleasant pain relief and sub-clinical psychological symptoms

Significant correlations were found between mean pleasant pain relief and STAI-S (r= -0.402; p=0.038). No significant correlations were found between mean pleasant pain relief and BDI-II (r= 0.184; p=0.359) and mean pleasant pain relief and SHPS (r=-0.136; p=0.498). Finally, no significant correlations were found between BDI-II, STAI-S and SHPS and pain unpleasantness or pain intensity during the conditioning stimulus (p> 0.4).

4.4 Test-retest reliability

Reliability was evaluated for mean pain intensity and mean pain unpleasantness, taken during two separate administrations of the conditioning stimulus, as well as between each value of pleasant pain relief, taken 10s after each conditioning stimulus. The ICC correlations along with their 95% CI for mean pain intensity, mean pain unpleasantness and pleasant pain relief were

respectively ICC(1,1)=0.692; 95% CI=0.434-0.846, ICC(1,1)=0.870; 95% CI=0.738-0.939 and ICC(1,1)=0.638; 95% CI=0.35-0.816.

5. Discussion

The main objective of this study was to examine if there is a relationship between the ICPM efficacy and the pleasant pain relief experienced after the administration of the same conditioning stimulus used to trigger endogenous pain inhibition mechanisms. Associations between pleasant pain relief and other psychophysical measures and sub-clinical psychological symptoms were also examined. As shown by several previous investigations (Lewis, Heales, et al., 2012; Mlekusch et al., 2016; Yarnitsky, 2015) the conditioning stimulus (e.g. cold-pressor test) produces significant analgesia, as illustrated by a significant reduction in pain perception during the second test stimulus, compared to the first one. Our study showed that significant pleasure was experienced after the interruption of the conditioning stimulus. Greater pain intensity and unpleasantness during the conditioning stimulus was associated with greater pleasant pain relief. However, there was no correlation between ICPM efficacy and the magnitude of pleasant pain relief. Finally, we found that anxiety was negatively correlated with pleasant pain relief.

Prior to analyzing any potential association between ICPM efficacy and the magnitude of pleasant pain relief, it was important to first establish that the interruption of the conditioning stimulus produces significant pleasant pain relief. This was the case. Indeed, in addition to having the mean pleasant pain relief close to 40% and the peak pleasant pain relief close to 70%, the effect also lasted at least 4 minutes in most participants (at endpoint, the pleasant pain relief was 26.3%). By comparison, Lekness et al. (Leknes et al., 2008) measured pleasant pain relief

after the interruption of a 15 x 20 mm thermode on the left forehand of participants during 3 seconds and found that the peak pleasant pain relief was about 35%, and lasted about 8 seconds. As in the study from Lekness et al. (Leknes et al., 2008), we found that both pain intensity and unpleasantness during the conditioning stimulus were positively correlated with the magnitude of pleasant pain relief after cessation of the conditioning stimulus. Taken together, these results strengthen the validity of using the cold-pressor test as a conditioning stimulus to elicit pleasant pain relief.

Although the conditioning stimulus elicited strong pleasant pain relief and significant ICPM, pleasant pain relief and ICPM were not significantly correlated. From a methodological point of view, this is an important observation, considering that several teams of investigators use *sequential* ICPM paradigms (Drummond & Knudsen, 2011; Leonard et al., 2009; Potvin & Marchand, 2016b). A significant positive correlation between the two phenomena would have suggested that the analgesic effects triggered by the conditioning stimulus could be confounded by pleasant pain relief triggered at the end of the conditioning stimulus. The lack of correlation observed here suggests that ICPM assessment is not significantly confounded by the pleasant pain relief effect, although both phenomena co-occur in time.

Another implication of the current study lies in the fact that it provides a new potential explanation for the strong link between pain and anxiety. Although we found no significant relationship in the current study, several previous experimental studies have shown that noxious stimuli cause anxiety, and that anxiety increases pain perception in healthy volunteers (KC Prabhat, Sandhya Maheshwari, Sanjeev K Verma, ND Gupta, A Balamani, Mohd Tauseef Khan, 2014; Nahman-Averbuch et al., 2013; Rhudy & Meagher, 2000). At the moment, however, the reasons for the association between pain and anxiety remain elusive. Despite inconsistent

results, some studies have found a negative association between anxiety and the ability to experience pleasure (Cremers, Veer, Spinhoven, Rombouts, & Roelofs, 2015; Dillon et al., 2008). Comparatively, the link between anxiety and pleasure has been less investigated in experimental settings. Therefore, the finding of a negative correlation between pleasant pain relief and anxiety, as observed in the current study, suggests that anxiety acutely disrupts the homeostatic balance between pleasure and pain. Conversely, a lower ability to experience pleasant pain relief may have caused participants to feel more anxious.

The current study has a few limitations. Firstly, the most prolonged measure of pleasant pain relief (e.g. 240 seconds) was not assessed at the same time as endogenous pain inhibition. However, we found no correlation between pleasant pain relief and ICPM efficacy event when we used the first assessment of pleasant pain relief (e.g. after the first of the conditioning stimulus). This makes it unlikely that the lack of correlation between ICPM efficacy and pleasant pain relief would be confounded by the passage of time. Another limitation of the current study is that the sample size could have been larger, meaning that the lack of correlation between ICPM and pain relief pleasantness could be explained by a lack of statistical power. However, this does not seem very likely given that the correlation between ICPM and pleasant pain relief was very weak. Another limitation has to do with the fact participants were explicitly introduced to the concept of pleasant pain relief before the experimental session, and this may have influenced participants' expectations of experiencing ICPM. Previous research has shown that the magnitude of ICPM is influenced by expectations (Goffaux, Redmond, Rainville, & Marchand, 2007). Finally, it is important to remember that the current study used a correlational design, which means that it cannot be concluded from the present results that pleasant pain relief

and ICPM are independent phenomena. The experimental manipulation of variables would be required in order to reach a firm conclusion.

6. Conclusion

The current study showed, for the first time, that strong feelings of pleasantness are elicited after the cessation of the conditioning stimulus and that ICPM and pleasant pain relief both co-occur but are not significantly correlated. These results provide support for the use of the cold-pressor test as a conditioning stimulus to study pleasant pain relief and suggest that the results of *sequential* ICPM paradigms are not strongly confounded by co-occurring pleasant pain relief. The current results also provide novel insights on the complex link between anxiety and pain perception. Future studies will need to examine the influence of psychophysical properties of nociceptive stimuli (e.g. spatial and temporal summation) on the magnitude of pleasant paint relief and to investigate the neural pathways that are specifically and/or commonly involved in ICPM and pleasant pain relief. Finally, the precise influence of anxiety on pleasant pain relief will need to be determined.

Abbreviation

ICPM: Inhibitory conditioned pain modulation

Data availability

To insure participant privacy, data will not be made available given that genetic has also been collected as part of this study.

Conflict of interest

Authors declare no conflicts of interest.

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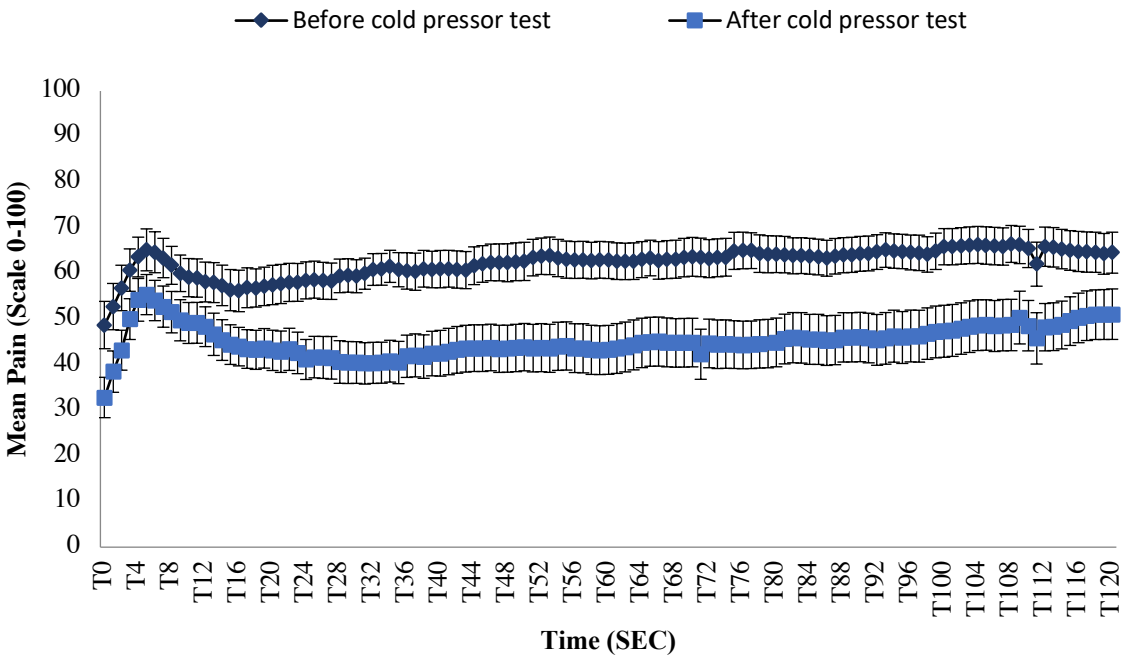
Table 1: Characteristics of the participants

Characteristics	M / %
Age (M ± SEM)	25.1 ± 0.82
Sex (%)	
Male	40.6
Female	43.8
Ethnicity (%)	
Caucasian	50
Afro-American	6.3
Latin-American	3.1
Asian	6.3
Other	18.8
Level of education (%)	
College degree	15.6
Bachelor's degree	40.6
Graduate studies	28.1
Employment status (%)	
Employed	46.9
Unemployed	6.3
Loan or bursary	15.6
Other (i.e. independent worker, welfare)	15.6
Psychological symptoms (M ± SEM)	
BDI-II	5.11 ± 1.07
STAI-S	46.68 ± 0.83
SHPS	48.81 ± 0.65

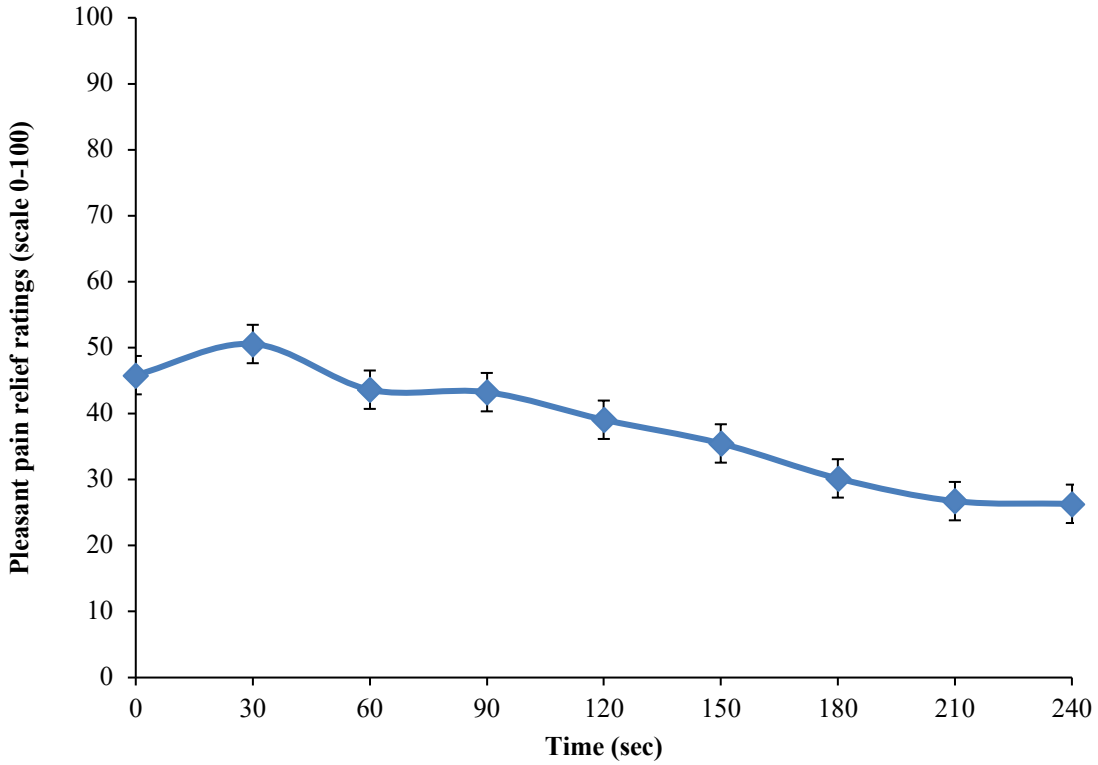
BDI-II= Beck Depression Inventory; SHPS= Snaith-Hamilton Pleasure Scale; STAI= State and Trait Inventory; SEM= standard error of the mean; M= mean.

Figure 1: Inhibitory conditioned pain modulation



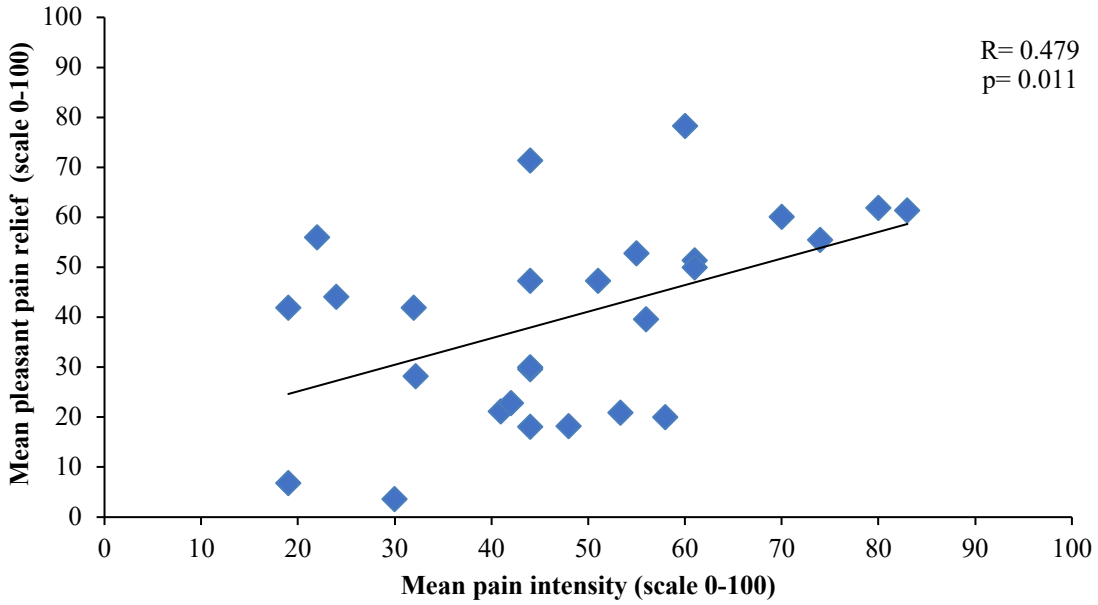
Legend: This figure shows the pain perception of participants during both administrations of the test stimulus for 2 minutes (120 seconds). Pain perception during the test stimulus was evaluated twice, once before (in dark blue) and once after (in pale blue) the administration of the conditioning stimulus. Each time point shows the mean and SEM.

Figure 2: Perception of pleasant pain relief during 240 seconds



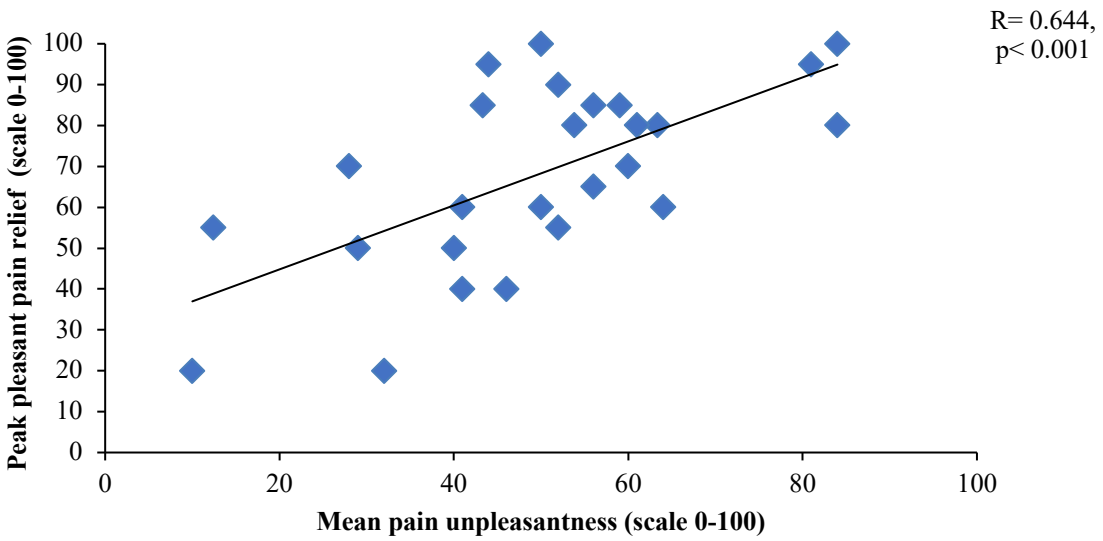
Legend: This figure illustrates the pleasant pain relief reported by participants for 4 minutes following the second administration of the conditioning stimulus. The mean and SEM is displayed for each time point.

Figure 3: Correlation between pain intensity during the cold pressor test and mean pleasant pain relief



Legend: This figure illustrates the correlation between the mean pain intensity during the second application of the conditioning stimulus, and mean pleasant pain relief, measured following the second conditioning stimulus.

Figure 4: Correlation between pain unpleasantness during the cold pressor test and peak pleasant pain relief



Legend: This figure illustrates the correlation between the mean pain unpleasantness during the second application of the conditioning stimulus, and peak pleasant pain relief, measured following the second conditioning stimulus.

Chapter 3: Methodology for study 2

3.1 Participants

Following our first psychophysical study, a second study was conducted with 26 subjects. In study 2 we further extend the first study by observing all cerebral activations/deactivation during pain onset and by investigating all possible relationships between brain activations and de-activations during pain onset with pain perception, pleasant pain relief and subclinical psychological symptoms. This study was comprised of two sessions; a psychophysical session and an fMRI session. During the psychophysical session, the exact same procedure as explained in the article above was used to measure four psychophysical measures; the *inhibitory conditioned pain modulation* paradigm, pain intensity, pain unpleasantness and pleasant pain relief.

For the fMRI segment of this research, 26 (15 women) healthy subjects were recruited between the ages of 18 and 35 (25 ± 1.12, mean ± standard error of the mean (SEM)). Of these 26 subjects, three were returning participants and 23 were new subjects. Recruitment was done via online advertisements (school platforms and Kijiji) and through word of mouth. The exclusion criteria were the following; (1) any DSM-V axis psychiatric disorder (2) centrally acting medication (3) neurologic disorders (4) any unstable medical conditions (including chronic pain) and (5) fMRI contraindications (e.g. metal or electronic implant or pregnancy).

3.2 Clinical assessment

The subclinical psychological conditions were evaluated using the *Beck depression inventory* (BDI) (Cronbach's α 0.90 and Pearson r= 0.73-0.96), the *State and Trait Anxiety*

Inventor-State subscale (STAI-S) (Cronbach's α 0.93 and Pearson r= 0.70), the *Snaith-Hamilton Pleasure Scale* (SHPS) (Cronbach's α 0.80 and Pearson r= 0.70), the *Community Assessment of Psychic Experiences* (Cronbach's α 0.78 and Pearson r= 0.80) and the presence of acute pain was measured using the *Brief Pain Inventory* (BPI) (Cronbach's α 0.86-0.96 and Pearson r= 0.67-0.93) (Barnes, Harp, & Jung Sik, 2002; Brenner et al., 2007; Franken, Rassin, & Muris, 2007; Loas et al., 1997; T. Mendoza, Mayne, Rublee, & Cleeland, 2006; Schlier, Jaya, Moritz, & Lincoln, 2015; Wang & Gorenstein, 2013).

The BDI questionnaire is comprised of 21 questions on a 4-point Likert scale ranging from 0-3. The sum of all 21 questions was used for analysis (Sprinkle et al., 2002). The STAI-S questionnaire is composed of 20 questions on a 4-point Likert scale ranging from 1 (almost never)- 4 (almost always). The sum of the score of all 20 questions was used for analysis (Julian, 2011). The SHPS questionnaire is composed of 14 questions, each raging from 1 (strongly disagree)- 4 (strongly agree). The sum of each question was used for analysis (R. P. Snaith, M. Hamilton, S. Morley, A. Humayan, 1995). The CAPE questionnaire is comprised of 42 questions and is subdivided into three subscales; positive symptom subscale (20 questions), negative symptom subscale (14 questions) and the depression subscale (8 questions). Each question is on a 4-point Likert scale and measures the level of distress of the symptoms 1 (not distressed)- 4 (very distressed) and the frequency of the symptoms 1 (Never)- 4 (nearly always). This questionnaire is analyzed with the mean total score and the mean score for each individual subscale (Mossaheb et al., 2012). The BPI is composed of two subscales; pain severity and pain interference. The pain severity subscale is comprised of four questions on a 10-point scale ranging from 0 (no pain)- 10 (pain has been as bad as you can imagine). The sum of all four items was used for analysis. The pain interference subscale measures how pain interferes with

7 different daily activities. All 7 items of this subscales are on a 10-point scale ranging from 0 (does not interfere)- 10 (completely interferes). The sum of all 7 scores was used for analysis (Cimino Brown, 2017).

3.3 Stimulus

The CPT is a widely used technique for testing pain paradigms (Kennedy et al., 2016a; Marchand & Arsenault, 2002). This test is preferred over others, such as the thermode, mainly for its ability to induce pain over a large surface of the skin (spatial summation) (Marchand & Arsenault, 2002). The CPT induces pain immediately once the limb is immerged into the water and the overall pain intensity ratings are significantly greater for the CPT than for the thermode (Lapotka et al., 2016; Ruscheweyh, Stumpenhorst, Knecht, & Marziniak, 2010). Unfortunately, because the CPT is comprised of water, it causes a problem when testing in fMRI settings. Indeed, the presence of water around expensive machinery causes a major concern. For this reason, some research teams have opted for alternatives, such as bags of ice water or the cold pressor gel test (Lapotka et al., 2016; Sprenger et al., 2011). Still, experimental procedures involving bags of water don't fully eliminate the risk of damage caused by water. For this reason, our research team opted for a modified CPT using gelled water. Precisely, a gel was prepared using the same protocol as explained by Lapotka et al., (2016). Once the gel was prepared, it was placed into plastic bags (4 x 11 inch's). Two stimuli were used during the experiment; a cold stimulus (inducing pain) and a control stimulus (inducing no pain). For the pain-inducing stimulus, the bags of gel were placed into a -10°C freezer. The temperature of the bags was precisely **0°C** and was maintained at that temperature during the whole procedure. We conducted preliminary testing on 10 individuals and were able determined that the gel maintains

its temperature for the entire duration of the testing, that the stimulus was safe (no chilblain) and was painful but tolerable (induce 50% pain on a scale from 0 no pain-100 most intense pain tolerable). On the other hand, the control stimulus was comprised of bags of g
el that was kept at room temperature (23°C).

3.4 Experimental design

3.4.1 Stimulus presentation

In a previous study, a research investigated brain activations to painful stimuli by administering a noxious cold stimulus (2°C) for 40 s (Kwan, Crawley, Mikulis, & Davis, 2000). Furthermore, a study administering a noxious heat stimulus for up to five minutes saw no effects of habituation and another study administering a noxious cold stimulus for 1 minute also had no effects of habituation (J. C.W. Brooks et al., 2005; La Cesa et al., 2014). Similarly, our study administered a modified CPT of 0°C for 45 seconds. More precisely, we administered the modified CPT during two separate runs. Each run lasted three minutes and was divided into four blocks (45 seconds per block). During the first and third block (45s each), no stimulus was administered (rest block). During the second and fourth blocks (45s each), either a cold stimulus (pain block) or a control stimulus (control block) were applied. The order of presentation of each stimulus (cold or control) changed between each run. More precisely, if the first run was as follows; rest-pain-rest-control, then the second run was; rest-control-rest-pain. To the opposite, if the first run was rest-control-rest-pain, then the second run was rest-pain-rest-control. The order of each block in each run was counterbalanced between participants. Furthermore, studies have included a five-minute time gap between runs to avoid pain sensitization or habituation (La Cesa et al., 2014; Leknes et al., 2008). Likewise, we conducted

preliminary tests that insured there was no pain sensitization with a 10-minute interval between each run (during this time gap, T1 images were acquired). Finally, a new bag of control stimulus and pain stimulus was used for each run. While a research assistant manipulated the bags of gel on the participants' **right foot**, participants were asked to lie supine fixating a black screen with a white cross in the middle. An example of the presentation of each run is detailed in figure 2.

3.4.2 Subjective measurements

During the scanning period, pain intensity and pleasant pain relief were both verbally measured by participants on a scale of 0 (no pain/no pleasant pain relief)-100 (maximum pain tolerable/maximum pleasant pain relief). Two different reviews have identified that using the numerical scale 0-10/0-100 is the most commonly used numerical scale for measuring pain/pleasure, mainly because it is simple and easy to explain/understand (Cheng & Rosenquist, 2018; Racine et al., 2012). It has been noted that pleasant pain relief diminishes over time. For this reason, it was important to take this measurement immediately after the offset of the painful stimulus. Therefore, pleasant pain relief was only measured in runs with pain administered in the fourth block (block four = pain block). Finally, after each run, participants were also asked to verbally rate the intensity of the pain bloc.

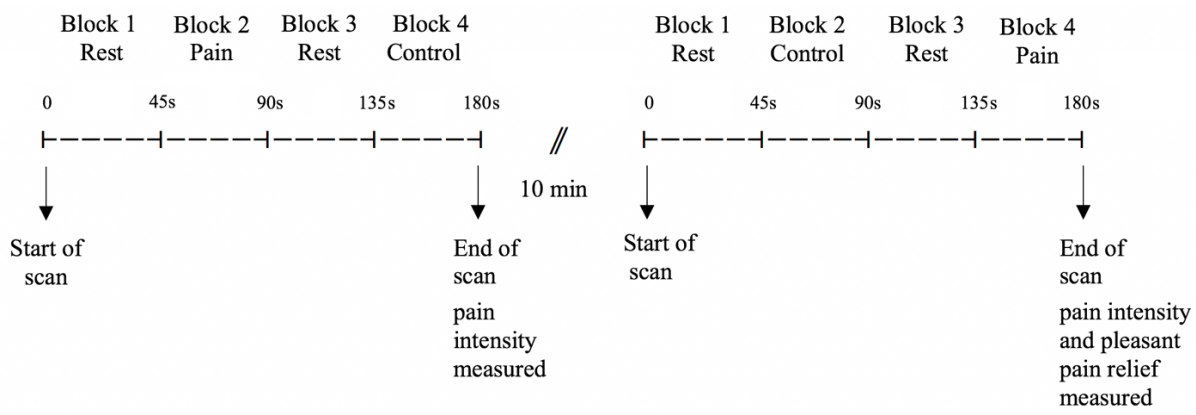


Figure 2. Stimulus presentation. Each run lasted three minutes and was comprised of four 45 second blocs. There was a 10-minute interval between each run to insure no pain sensitization. The order of the administration of each stimulus in each run was counterbalanced between each participant.

3.5 MRI acquisitions parameters

Whole brain fMRI was performed on a Prisma Fit 3.0 Tesla scanner from Siemens at the *Unité de Neuroimagerie Fonctionnelle de l'Institut de Gériatrie de l'Université de Montréal* using echoplanar imaging measuring blood oxygenated level dependent signal (BOLD). Functional images were acquired by a T2-weighted multiband echoplanar imaging (EPI) sequence (TR 785 ms; TE 30 ms; FA=54°; matrix size 64x64, voxel size 3 mm^3; 42 slices). These slices were oriented in transverse plane and were angled to be parallel to the AC-PC line. An inline retrospective motion correction algorithm was employed while the EPI images were acquired. During the same scanning session, T1-weighted anatomical images were also acquired for each subject (TR 2300ms; TE 2.98ms; FA 9°; matrix size 256x256; voxel size 1 mm^3; 176 slices).

3.6 Processing of fMRI images

fMRI data was preprocessed using CONN functional connectivity software version 17 (Whitfield-Gabrieli & Nieto-Castanon, 2012). This software uses functions from the *Statistical Parametric Mapping 12* (SPM12) software running in Matlab2017a (Ashburner et al., 2016; Simpson, Devenyi, Jezzard, Hennessy, & Near, 2017). Functional images were realigned, motion corrected using *Artifact Detection Tools* implemented in CONN (setting a threshold of 0.9 mm for subject motion and a global signal threshold of Z=5), high-pass filtered (0.008 Hz), centred, slice-time corrected and co-registered to their corresponding anatomical images. Anatomical images were normalized to the *Montreal Neurological Institute* (MNI) stereotaxic space. Afterwards, functional images were normalized to the MNI space from their corresponding anatomical images, a 3D isotropic Gaussian Kernel (8mm full-width at half maximum) was used for spatial smoothing and finally voxels were resliced to 2 mm^2 voxels.

Changes in BOLD activation between the pain condition and the control condition were analyzed on a block design basis by using a general linear model (GLM) in SPM12. The two experimental conditions (pain vs control) were defined as predicters of interest and the blocks for each condition were combined. A single-subject GLM was conducted, in which both conditions (pain and control) were entered as fixed factors. The parameters of this model were entered into a random-effect model that was used for group analysis using a one-sample t-test. Two contrasts were analyzed; pain > control and control > pain. Cluster activation was considered significant at $p < 0.001$ uncorrected with minimal cluster threshold of 50. Beta values for each significant cluster was extracted.

3.7 Statistical analysis

3.7.1 Psychophysical data

First, the Shapiro-Wilk test was used to assess normality for all the questionnaires that were administered (BDI, STAI-S, SHPS, CAPE and BPI). All questionnaires followed a normal distribution expect for the BDI, the CAPE depression subscale and the BPI pain interference subscale.

Second, as previously mentioned, during *the psychophysical session*, pain intensity, pain unpleasantness and pleasant pain relief were each measured twice. To ensure the test-retest reliability of this measure, an interclass correlation coefficient (ICC) with a 95% confidence interval (CI) was calculated. The ICC was a one-way random effect model with single measures. Values of ICC inferior to 0.5 have poor reliability, values between 0.5 and 0.75 have moderate reliability and values superior to 0.75 have excellent reliability (Koo & Li, 2016b).

Finally, we tested relationships using Pearson correlations between the following variables (1) pain intensity with pleasant pain relief; (2) pain intensity with each questionnaire administered (BDI, CAPE, BPI, STAI-S and SNHP); (3) pain unpleasantness with pleasant pain relief; (4) pain unpleasantness with each questionnaire administered (BDI, CAPE, BPI, STAI-S and SNHP) and (5) pleasant pain relief with each questionnaire (BDI, CAPE, BPI, STAI-S and SNHP). Results are presented as mean ± standard error of the mean (SEM). All results presenting a $p < 0.05$ were considered significant. Analysis was conducted using SPSS, version 25.

3.7.2 fMRI analysis

Pain intensity was measured twice during the scanning session. Consequently, we measured the test-retest reliability using ICC. Furthermore, we tested relationships between the variables collected during the fMRI session (pain intensity and pleasant pain relief) with the variables collected in the psychophysical session (pain intensity, pain unpleasantness and pleasant pain relief) using Pearson correlations. Finally, we tested for possible correlations between the mean beta of each significant (de-)activation cluster and; (1) pain intensity; (2) pain unpleasantness; (3) pleasant pain relief and (4) each questionnaire administered (STAI, BDI, SNHP, CAPE and BPI). These relationships were considered significant at $p < 0.05$ and analysis was conducted using SPSS, version 25.

Chapter 4: Results of study 2

4.1 Demographic results

Demographic and subclinical psychological results are presented in table 1.

Table 1. Participant characteristics

Characteristics	Statistics
Age (M±SEM)	25±1.12
Sex (N, %)	
Male	11 (42)
Female	15 (58)
Ethnicity (%)	
Caucasian	50
Afro-American	15
Asian	31
Arab	4
Level of education (%)	
College degree	58
Bachelor's degree	31

Graduate studies	11
Employment status (%)	
Employed	35
No income	19
Loan or bursary	23
Others (i.e. independent worker, welfare)	23
Psychological symptoms (M±SEM)	
BDI-II	5.35 ± 0.08
STAI-S	45.54 ± 0.26
SHPS	50 ± 0.12
CAPE Total	1.65 ± 0.08
Positive symptom frequency	1.37 ± 0.12
Positive symptom distress	1.5 ± 0.19
Negative symptom frequency	1.72 ± 0.16
Negative symptom distress	1.78 ± 0.18
Depression frequency	1.80 ± 0.21
Depression distress	2.08 ± 0.19
BPI*	
Pain severity	1.69 ± 0.77
Pain interference	1.55 ± 0.49

Abbreviation: BDI-II; Beck Depression Inventory-II, STAI-S; State and Trait Anxiety Inventory- State subscale, SHPS; Snaith-Hamilton Pleasure Scale, CAPE; Community Assessment of Psychic Experiences, BPI; Brief Pain Inventory.

* The type of pain that was reported by 13 participants was muscle pain caused by a workout. None of these participants were in pain at the tome of the testing.

4.2 Psychophysical session

4.2.1 Pain perception of the cold pressor test

During the laboratory session, participants performed two separate CPT. During each CPT, the scores for pain intensity and pain unpleasantness were taken at the moment the participants placed their arm into the water and then after every 30 seconds, for 120 seconds. During the first CPT, the averages for pain intensity and pain unpleasantness were respectively 48.88 ± 3.90 and 49.12 ± 4.35 and the average score of pain intensity and pain unpleasantness

at 120 seconds were respectively 58.08 ± 5.00 and 60.38 ± 5.20. During the second CPT, the averages for pain intensity and pain unpleasantness were respectively 45.92 ± 4.31 and 47.30 ± 4.60 and the average score of pain intensity and pain unpleasantness at 120 seconds were respectively 58.84 ± 5.30 and 59.00 ± 5.60. The were no significant difference between the average *pain intensity* and *pain unpleasantness* during the first and second administration of the CPT (respectively $t(25)= 1.64$, $p=0.12$ and $t(25)=0.91$, $p=0.37$.

4.2.2 Pleasant pain relief

Pleasant pain relief was measured after each CPT in *the psychophysical session*. After the first CPT, the pleasant pain relief was measured once (57.31 ± 5.53). After the second CPT, the pleasant pain relief was measured every 30 seconds for four minutes. The average score (ranging from 0-100) for pleasant pain relief taken every 30 secondes for 4 minutes was 42.53 ± 4.26.

4.2.3 Test-retest reliability

Test-retest reliability was measured for the following variables during the *psychophysical session*; mean pain intensity (ICC (1,1) = 0.90, 95% CI= 0.79-0.95), mean pain unpleasantness (ICC (1,1) = 0.90, 95% CI= 0.80-0.95) and pleasant pain relief (ICC (1,1) = 0.80, 95% CI= 0.61-0.91). Test-retest reliability was also measured for pain intensity during the *scanning session* (ICC (1,1) = 0.88, 95% CI= 0.75-0.94).

4.2.4 Correlations between pain perception and pleasant pain relief taken during the psychophysical session

There was a significant correlation between the average pain intensity and the average pleasant pain relief (r= 0.563, p= 0.003) and between the average pain unpleasantness and the average pleasant pain relief (r= 0.517, p= 0.007). Both of these correlations were found with the measures taken during the *second* administration of the CPT. However, no correlations were found between pain intensity and pleasant pain relief (r=0.32, p=0.11) or between pain unpleasantness and pleasant pain relief during the first CPT (r=0.38, p=0.054) in *the psychophysical session*. However, pleasant pain relief was only measured once after the first CPT, we believe that the lack of correlation here is due to the lack of statistical power.

4.2.5 Correlations between subclinical psychological symptoms and psychophysical measures taken during the psychophysical session

No correlations were found between any questionnaires (STAI-S BDI, SNHP, CAPE and BPI) and pain intensity, pain unpleasantness or pleasant pain relief for the *first* and *second* CPT in *the psychophysical session* (all p-values > 0.09).

4.3 fMRI session

4.3.1 Pain perception of the modified cold pressor test during the fMRI session

During *the fMRI session*, a modified CPT (gel) was administered twice. The pain intensity of the modified CPT during the *first* and *second* administration was respectively 56.19 ± 5.54 and 56.15 ± 5.72.

4.3.2 Pleasant pain relief

As mentioned, during *the fMRI session*, pleasant pain relief was only measured when a painful stimulus was presented in the fourth block. The average pleasant pain relief during *the fMRI session* was 44.5 ± 5.54.

4.3.3 Correlations between pain intensity and pleasant pain relief taken during the fMRI session

Pain intensity was measured after each administered modified CPT (gel) during *the fMRI session*. However, for the following correlation, only the measures of pain intensity taken when a painful stimulus was administered in the fourth block was used. Therefore, the correlation between pleasant pain relief and pain intensity was r= 0.602, p= 0.001 (figure 3).

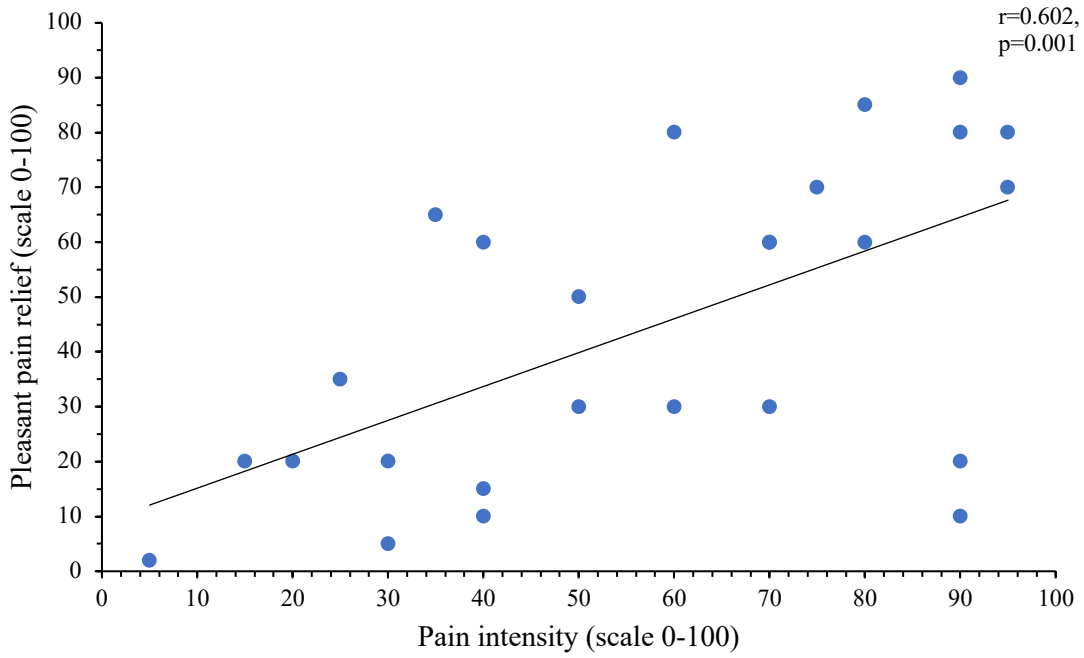


Figure 3. Correlation between pain intensity and pleasant pain relief during the modified CPT (gel) in the fMRI session.

4.3.4 Correlations between psychophysical measures taken during the fMRI session and subclinical psychological symptoms

Significant correlations were found between pain intensity during the *first* and *second* modified CPT (gel) and BPI pain interference subscale (respectively; r=0.439, p=0.025 and r=0.483, p=0.012). There were no other significant correlations found between pain intensity of the modified CPT and any other subclinical psychological symptoms measured by the STAI-S, BDI, SNHP the CAPE and BPI pain severity subscale.

A significant correlation was also found between pleasant pain relief in *the fMRI session* and BPI pain severity subscale (r=0.453, p=0.02). There were no correlations between pleasant pain relief and the STAI-S, BDI, SNHP the CAPE or the BPI pain interference subscale.

4.3.5 fMRI BOLD activation

Two contrasts were analyzed; pain > control and control > pain. In the pain > control contrast, four brain regions were significantly activated during the modified CPT (gel); the left insula, the left precuneus, the left middle frontal gyrus (MFG) and the right lingual gyrus (table 2 and figure 4). The second contrast, control > pain, showed a de-activation in the right medial orbital frontal gyrus during the administration of the pain stimulus (mean beta 0.36 ± 0.09) (figure 4 and 5). To better understand the effect resulting from the medial orbital frontal cortex, beta values from this region were then extracted during the pain condition and the control condition independently using *MarsBar* toolbox on SPM (Brett, Anton, Valabregue, & Poline, 2002). As shown in figure 5, subjects exhibited a significantly reduced activation in the pain condition (mean beta -0.41 ± 0.11).

Table 2. Activation clusters

Contrast	Brain region	L/R	BA	MNI			Voxel size	t-value	p value of cluster
				x	y	z			
pain>ctl									
	Insula	**L**	13	**-34**	**6**	**10**	**6349**	**8.89**	**< 0.001**
	Putamen	L		-24	4	10		8.09	
	Caudate nucleus	L		-18	-26	22		7.28	
	Thalamus	L/R		-6	-26	12		7.49	
	Insula	L/R		-30	-26	16		6.93	
	Precuneus	**L**		**-6**	**-42**	**64**	**1504**	**5.54**	**< 0.001**
	Paracentrale lobule	L		-4	-28	72		4.57	
	Middle frontal gyrus	**L**		**-30**	**40**	**22**	**122**	**4.7**	**< 0.001**
	Lingual Gyrus	**R**		**18**	**-78**	**10**	**272**	**4.47**	**< 0.001**
ctl>pain									
	medial orbital	**R**	11	**6**	**24**	**-12**	**129**	**4.38**	**< 0.001**

Abbreviation: L; left, R; right, BA; Brodmann area, SPM; Statistical Parametric Mapping

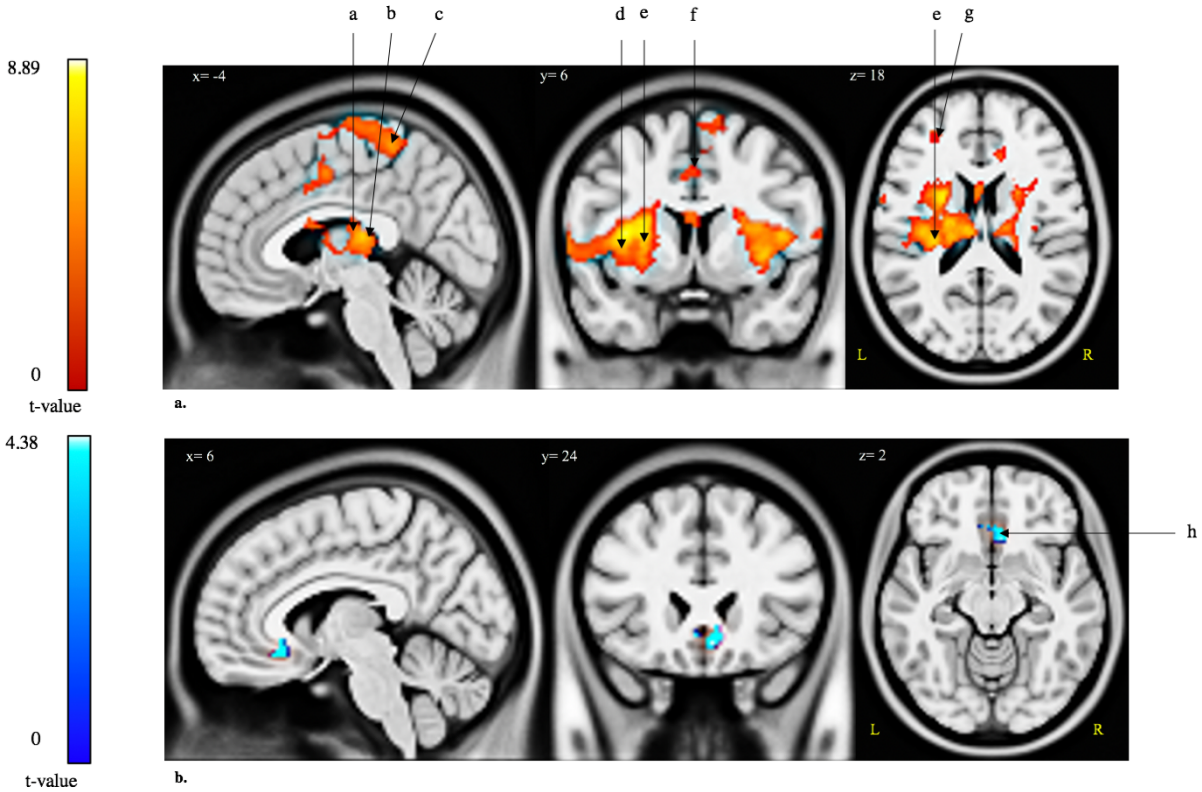


Figure 4. Cluster activations. In one fMRI session, there were two runs. Each run was comprised of a 45 second pain block and a 45 second control block. Each 45 second pain block of each run were combined together and each 45 second control block of each run were also combined together. Two contrasts were analysed pain > control and control > pain. a. Activations in the contrast pain > control. This illustration shows hyperactivations during the administration of the pain stimulus compared to the administration of a control stimulus. b. Activations in the contrast control > pain. This illustration shows a hypoactivation during the administration of a control stimulus compared to the administration of a pain stimulus.

Abbreviation: a; L-middle caudate nucleus, b; L/R-posterior thalamus, c; L-paracentral lobule, d; L/R-insula, e: L-putamen, f; L-precuneus, g; L-middle frontal gyrus, h; R-medial orbital frontal gyrus.

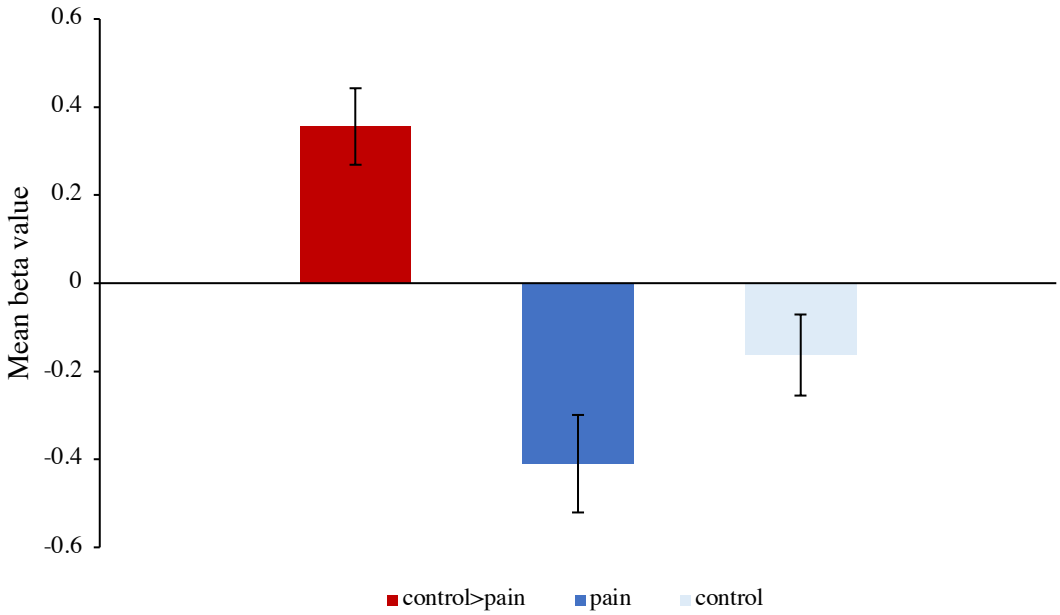


Figure 5. Mean beta. Three mean beta values were extracted for the right medial orbital frontal gyrus in the control>pain contrast. The average beta value for the contrast control>pain (red) was 0.35 ± 0.09, the average beta value for this contrast during painful stimulation (dark blue) was -0.41 ± 0.11 and during the administration of the control stimulus (light blue) was -0.16 ± 0.09. These negative values show deactivation in the right medial orbital frontal gyrus during both the pain and the control stimuli. However, the deactivation was greater during the painful stimulation.

4.4 Correlational analyses with significant brain activations

4.4.1 Correlation between psychophysical results and beta values

The correlations between psychophysical measures (pain intensity, pain unpleasantness and pleasant pain relief) taken throughout both sessions (psychophysical and fMRI) and beta values of the insula, the precuneus, the MFG and the medial orbital frontal gyrus were calculated and are presented here.

During *the fMRI session,* the mean beta value of the **insula** was significantly correlated with **pain intensity** during the *first* administration of the modified CPT (r=0.475, p=0.014) and the **precuneus** was significantly correlated with **pain intensity** measured during *the first* and *second* administration of the modified CPT (respectively; r=0.599, p=0.001 and r=0.448, p=0.022).

During *the psychophysical session*, pain unpleasantness, pain intensity and pleasant pain relief were measured twice. **Firstly**, the **average pain unpleasantness** during the *first* CPT in the *psychophysical session* significantly correlated with the mean beta value of the **insula** (r=0.405, p=0.04). **Secondly**, the **average pleasant pain relief** measured after the *second* CPT in the *psychophysical session* significantly correlated with the mean beta value of the **insula** (r=0.739, p<0.001), the **precuneus** (r=0.724, p<0.001) and the **MFG** (r=0.551, p=0.004). Finally, the medial orbital frontal gyrus did not correlate with any of the psychophysical measures that were taken during either experimental sessions.

4.4.2 Correlations between subclinical psychological symptoms and beta values

The BPI pain interference subscale questionnaire was significantly negatively correlated with the **right medial orbital frontal gyrus** during pain administration (-0.595, p=0.001) (figure 6.a) and positively correlated with the **left precuneus** (r=0.415, p=0.035) (figure 6.b). No other significant correlations were found between all other activation clusters and subclinical psychological symptoms measured by the STAI, BDI, SNHP the CAPE.

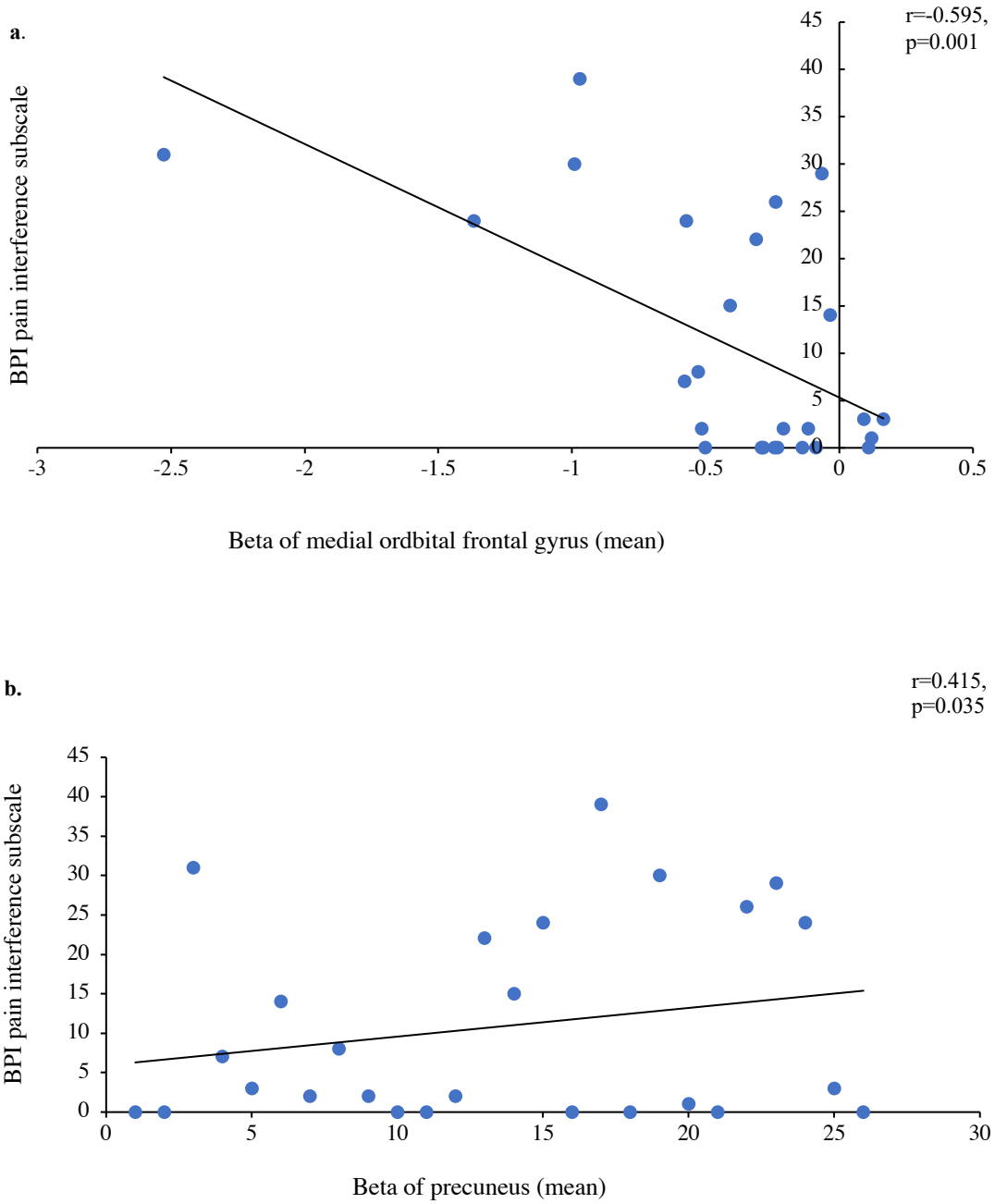


Figure 6. Correlation between the average beta values of the medial orbital frontal gyrus (figure 6.a.) and the precuneus (figure 6.b.) with the BPI questionnaire (pain interference subscale). a. This figure illustrates a negative significant correlation between the medial orbital frontal gyrus during a painful stimulation and the pain interference subscale of the BPI questionnaire. b. This figure illustrates a positive significant correlation between the precuneus during a painful stimulation and the pain interference subscale of the BPI questionnaire. **Abbreviation:** BPI; Brief pain inventory

Chapter 5. Discussion

Pain caused by any form of nociception is generally considered intrinsically aversive and unpleasant (Leknes et al., 2012). As per mentioned, the *International Association for the study of Pain* currently defines pain as a stressful, unpleasant and emotional experience, involving either actual or potential tissues damage (Williams & Craig, 2016). At the emotional level, pain perception tends to cause distress and to decrease feelings of pleasure. In fact, anhedonia, depression and anxiety have all been observed in patients suffering from chronic pain conditions (Garland, Trøstheim, Eikemo, Ernst, & Leknes, 2019). The consequences related to pain also include physical (e.g. difficulty walking) and social disruptions, all causing a significant financial burden to the patients and to society (Cheng & Rosenquist, 2018). One important phenomenon that has been greatly used to investigate the neurobiological bases of chronic pain is the ICPM phenomenon (Marchand, 2008). In fact, several clinical studies using ICPM paradigms have demonstrated that endogenous pain inhibitory mechanisms are significantly less effective in some chronic pain populations (e.g. fibromyalgia, migraine and irritable bowel syndrome) than in healthy individuals (Staud et al., 2003). ICPM paradigms allow us to measure diffused pain reduction triggered by an intense and prolonged painful stimulation on a large surface of the body (Marchand, 2008). Unfortunately, the pain reduction triggered by ICPM paradigms may actually be explained by another phenomenon that has been recently uncovered, namely pleasant pain relief. During nociceptive stimulation, the feeling of pleasure is attenuated (and presumably, the brain reward system is deactivated) (Leknes et al., 2008). Moreover, as explained by the *opponent process theory*, the painful stimulation also causes a deviation from homeostasis such that following the offset of the painful stimulation, a sensation of the opposite valence will be experienced, a pleasant sensation, in order to restore

homeostasis (Leknes et al., 2008). Considering that pleasant stimuli are well-known for causing hypoalgesic effects, it is therefore possible that the pain reduction measured by certain ICPM paradigms may be confounded by the pleasant pain relief phenomenon. In order to investigate the complex interactions between pain and pleasure, we conducted 2 separate studies investigating their psychophysical and neurobiological correlates during pain offset (study 1) and during pain onset (study 2).

In **study 1,** we had a particular interest in the interaction between the ICPM system and pleasant pain relief. Pain offset causes sensations of pleasure (i.e. pleasant pain relief), which in turn reduces pain sensations (Leknes et al., 2011). Therefore, we hypothesized that the analgesia measured in the ICPM phenomenon may be confounded by pleasant pain relief. For the investigation of ICPM, we employed the sequential paradigm instead of the parallel paradigm, mainly because it is still unclear if distraction is a confounding factor in the parallel paradigm. We then sought to evaluate if the sequential paradigm truly measured ICPM or pleasant pain relief. In this study, ICPM was measured using a test stimulus consisting of continuous heat applied using a Peltier thermode, applied before and after a conditioning stimulus consisting of continuous cold stimulation using the CPT. Pleasant pain relief was also measured after the interruption of the CPT. In this study, we found no correlation between the ICPM phenomenon and pleasant pain relief.

Whereas **study 1** was mainly interested in the reward system at pain **offset**, **study 2**, on the other hand, was mainly focused on evaluating the reward system during pain **onset**. According to the *opponent process theory*, pain ***onset*** causes disruption in our homeostasis and a decrease in pleasant sensations (Leknes et al., 2008). Hence, from a neurobiological perspective, we hypothesized that we would observe a decrease in the activity of the brain

reward regions during pain onset. fMRI studies applying pain using a thermode have failed to show this in a consistent manner (Leknes et al., 2012; Schnitzler & Ploner, 2000). Consequently, in study 2, we opted for a modified CPT, since the paradigm can be used to elicit both spatial and temporal summation (Marchand & Arsenault, 2002). More precisely, we applied noxious pain using a newly developed and modified CPT consisting of bags of gelled water at 0°C placed on participants' right foot during an fMRI scanning session. The results of this study successfully showed significant brain activations in the insula, the precuneus, the MFG and the lingual gyrus and a significant deactivation in the medial orbital frontal gyrus during painful stimulation.

5.1 Study 1

Pain is a dynamic phenomenon that uses both inhibitory and excitatory mechanisms, including the ICPM phenomenon (Marchand, 2008). This phenomenon postulates that a nociceptive stimulation will diminish or inhibit a second nociceptive stimulation if it produces both spatial and temporal summation and if it is located on a distant area from the first stimulation. Finally, this inhibition would be diffused over the whole body (Marchand, 2008). This phenomenon has been greatly used in clinical research to elucidate the neurobiological bases of chronic pain (Potvin & Marchand, 2016a; Yarnitsky, 2010). In fact, several experimental studies have shown that ICPM is disrupted in chronic pain conditions such as fibromyalgia, neuropathic pain and irritable bowel syndrome (Alshelh et al., 2018; Lewis, Rice, & McNair, 2012b; Paul-Savoie et al., 2012). Given that ICPM paradigms are frequently used in clinical studies, we felt it was important to investigate the possibility that the analgesia measured

in the ICPM phenomenon may be influenced or triggered by the pleasant pain relief caused by pain offset. To do this, we used the CPT to elicit strong analgesia and strong pleasant pain relief.

Many previous investigations have shown that a strong conditioning stimulus, such as the CPT, produces significant analgesia (Marchand, 2008). In this study, we have equally illustrated a significant reduction in pain perception during the second administration of the test stimulus (e.g. thermode), when compared to the first administration. Furthermore, we sought to determine that the interruption of the conditioning stimulus would induce pleasant pain relief, a phenomenon proposed by the *opponent process theory* (Leknes et al., 2012). We found a mean pleasant pain relief of 40%, a peak of almost 70% and finally, pleasant pain relief lasted four minutes in the majority of participants. Importantly, the pleasant pain relief measured in this study was greater than the one measured by Leknes et al., (2008). In the latter study, pain was induced using a 15 x 20 mm thermode and the intensity of pleasant pain relief was about 35% and lasted roughly only 8 seconds. Additionally, our study also demonstrated that greater pain intensity or pain unpleasantness during the conditioning stimulus led to increased pleasant pain relief after noxious pain termination. Notably, no significant correlation was found between ICPM efficacy and pleasant pain relief in our own experiment. According to this result, although both pleasant pain relief and ICPM co-occurred at the same time, pleasant pain relief did not seem to be a confounding factor in the ICPM phenomenon. The analgesia effects triggered by ICPM may thus not be explained by pleasant pain relief. By observing no correlation between the two phenomena, we demonstrated the validity of using the sequential paradigm to measure ICPM, which is methodologically very important, as several research teams use the sequential paradigm to measure ICPM (Marchand & Arsenault, 2002; Pud et al., 2009a). Furthermore, our results also demonstrate the validity of using the CPT to elicit strong pleasant pain relief after

the interruption of the stimulation. Using the psychophysical results found, we then measured potential correlations between psychophysical measures and subclinical psychological measures. Anxiety was found to be negatively correlated with pleasant pain relief, which is in accordance with one of the main assumptions of the *opponent process theory*, namely that when an individual is in distress (e.g. during pain onset, for instance), their feelings of pleasure decrease. Although study 1 mainly focused on the phenomena occurring during pain offset, study 2 further investigated the previous assumption that pleasure is decreased during pain onset.

5.2 Study 2

Whereas study 1 investigated the pain/reward system during **pain offset**, which allowed us to analyse the pleasant pain relief phenomenon and its association with ICPM and subclinical measures, study 2 focused on **pain onset**, more particularly regarding its associated neurophysiology. The *opponent process theory* predicts that 1) pain onset would induce decreased pleasure and that 2) pain offset would induce a compensatory pleasurable experience (pleasant pain relief). The depressing effect of a nociceptive stimulation on the brain reward system has been mainly studied in animals. Studies conducted on rodents have indeed shown that nociceptive stimuli, like paw incisions for instance, can cause decreased activations in brain reward regions, such as the ventral striatum (Moerke & Negus, 2019; Negus, 2013). The few studies that have been conducted in humans have used thermodes to induce pain; however, these studies have been unable to consistently show a deactivation in brain reward regions during nociceptive stimulation (Leknes et al., 2012; Schnitzler & Ploner, 2000). Consequently, in study 2, we opted for a modified CPT because this paradigm produces both spatial and temporal

summation, and thus, it can elicit strong pain perception and strong pleasant pain relief. Indeed, the CPT has been shown to induce a stronger pain experience than the thermode (Lapotka et al., 2016; Ruscheweyh et al., 2010). We applied noxious pain using a newly developed and modified CPT consisting of bags of gelled water at 0°C placed on participants' right foot during an fMRI scanning session. This modified CPT is also safe to use in an fMRI paradigm as it eliminates the possibility of water spillage as well as being safe for participants.

By focussing on pain onset, we were able to evaluate if the brain reward system is deactivated during a painful stimulation, therefore empirically testing the **first prediction** proposed by the *opponent process theory.*

5.2.1 Psychophysical results

The modified CPT (gel) used in study 2 induced significant pain to participants (approximately 56/100 pain intensity). Moreover, in study 2, the interruption of pain induced by the modified CPT (gel) elicited 45/100 pleasant pain relief in participants. Here again, the amplitude of pleasant pain relief induced by the modified CPT (gel) was greater than the pleasant pain relief measured by Leknes et al., (2008) using a thermode. In addition, we also found a significant correlation between pain intensity induced by the modified CPT and pleasant pain relief measured after its administration ($r=0.602$, $p=0.001$), demonstrating that the stronger the pain perception, the stronger the pleasant pain relief will be. These findings of the pleasant pain relief phenomenon are particularly interesting as they illustrate that pleasant pain relief is experienced after pain is terminated to restore homeostasis that has been disbalanced during pain onset (Leknes et al., 2008).

5.2.2 fMRI results

Aside from our psychophysical findings, neurobiological findings were also achieved using the modified CPT during fMRI acquisition. With previous studies observing activations in the pain matrix during noxious pain stimulation using the classic CPT (cold water applied on the arm) mainly in the insula, the thalamus, the somatosensory cortex and the ACC, we expected to find similar activations using the modified CPT (gel) (Bogdanov et al., 2015; La Cesa et al., 2014; Petrovic, Petersson, Hansson, & Ingvar, 2004). Indeed, our study found significant activations in the bilateral insula, bilateral thalamus, left caudate nucleus, left putamen, left precuneus (extending to the left paracentral lobule), left MFG and the lingual gyrus during cold pain stimulation relative to the control condition. Notably, the activation found in the insula was very large (6349 voxels), therefore covering both, the anterior and the posterior insula. While the posterior insula is known to be involved in the sensory-discriminative component of pain (pain intensity and location), the anterior insula is known to be involved in the affective component of pain (pain unpleasantness) (J. Brooks & Tracey, 2005; Jonathan C.W. Brooks et al., 2002; K. B. Jensen et al., 2016). The relationship between pain and these regions were further corroborated by finding a correlation between pain intensity induced by the modified CPT (gel) and the mean beta value of the entire region activated in the insula (posterior and anterior) and of the *precuneus*. A significant correlation between the mean beta value of the entire region activated in the *insula* (posterior and anterior) and pain unpleasantness (affective measurement of pain) was likewise observed. Finally, the insula, the precuneus and the MFG all significantly correlated with the pleasant pain relief measured after the *second* CPT in the *psychophysical session*, again showing that the stronger the pain, the stronger the pleasant pain relief will be.

Past investigations on pain perception have highlighted two main findings. Firstly, activations in the pain matrix, such as the insula and the ACC, increase according to the intensity of the pain (Leknes et al., 2012). Secondly, the ventral medial prefrontal cortex and the nucleus accumbens, two core regions of the brain reward system, are activated during pain relief (after noxious heat), as predicted by the opponent process theory (Lino Becerra & Borsook, 2008; Leknes et al., 2012). Although these previous studies have highlighted the involvement of the reward system in pleasant pain relief, previous neuroimaging studies have failed to consistently show deactivations in these regions during pain onset. One possible reason for this inconsistency may be due to the type of noxious stimulus used in previous studies. Indeed, these studies have mainly used a thermode to induce noxious heat pain (Aharon, Becerraa, Chabris, & Borsooka, 2006; L. Becerra et al., 2013; Leknes et al., 2011). Our study, on the other hand, used a modified CPT (gel) and was able to observe a **significant deactivation in the medial orbital frontal gyrus**, which is the most **important finding** of Study 2. The medial orbital frontal cortex is one of two core brain regions involved in reward processing, the second is the ventral striatum (Leknes et al., 2012). These observations are in accordance with the *opponent process theory* suggesting that pain onset causes activations in the pain matrix and decreased activations in the reward regions of the brain (Leknes et al., 2008). Afterwards, following pain offset, the theory proposes activations in brain reward regions as a compensatory mechanism to restore homeostasis (Leknes et al., 2008).

To better understand the effect of the medial orbital frontal gyrus during painful stimulation, we further extracted beta values from this region during the pain condition and the control condition separately. Using these beta values, we then were able to carry out correlational analysis between beta values and the results of the questionnaires administered.

Using the results found in the BPI questionnaire (pain interference and pain severity), we found that the deactivation in the medial orbital frontal gyrus during pain onset was stronger in people experiencing higher levels of pain interference in daily activity. In accordance, a meta-analysis has demonstrated that individuals with chronic pain report significantly more anhedonia that healthy individuals (Garland et al., 2019). Therefore, this concluded that painful experiences induce depressed feelings of pleasure.

Taken together, our neurobiological results confirm the *opponent process theory*, in that, they show that part of the brain reward activity is down regulated during pain onset.

5.3 Theoretical and methodological implications

5.3.1 Theoretical implications

Taken together study 1 and study 2 allowed us to collect psychophysical and neurobiological results supporting the main assumptions of the *opponent process theory.* The aforementioned assumptions imply that we should observe a compensatory effect between pain onset and pain offset (Leknes et al., 2008). As illustrated in figures 7 and 8, at baseline, our body is at homeostasis. However, if a nociceptive stimulation is administered, it will not only be experienced as painful, but it will also disrupt our homeostasis, and cause reduced feelings of pleasure (dysphoria). At the neural level, during the nociceptive stimulation, we will observe activations of pain processing regions and de-activations in brain reward regions (L. Becerra et al., 2013; Lino Becerra & Borsook, 2008). Once the nociceptive stimulation is terminated, brain regions of the pain matrix will no longer be recruited, and brain reward regions will become significantly activated as a compensatory mechanism that helps prepare the return to

homeostasis. As a result, the subject will experience pleasant feelings of pain relief (Leknes et al., 2012).

In study 1, we established that pain offset induces significant pleasant pain relief. **In study 2**, we found that our modified CPT induced significant activations in the pain matrix and significant deactivations in one of the core reward regions, the medial orbital frontal gyrus. Indeed, a meta-analysis including 56 articles (768 coordinates) has highlighted the importance of the ventral medial prefrontal cortex/medial orbital frontal cortex in reward processing, precisely during reward receipt (e.g. monitory gain) (Diekhof, Kaps, Falkai, & Gruber, 2012). This finding was one of our most important finding because, unlike past research, we showed that pain onset causes a deactivation of one of the main brain reward regions.

The relationship between the pain and reward system may explain why certain physical and affective comorbidities tend to co-occur, such as chronic pain and depression (Garland et al., 2019). In fact, clinical studies have observed anhedonia in people suffering from chronic pain (Elvemo, Landrø, Borchgrevink, & Haberg, 2015; Garland et al., 2019). Interestingly, studies investigating the relationship between pain and pleasure in humans have mainly focused on clinical observations, meaning that biological mechanisms involved in these comorbid conditions are poorly understood.

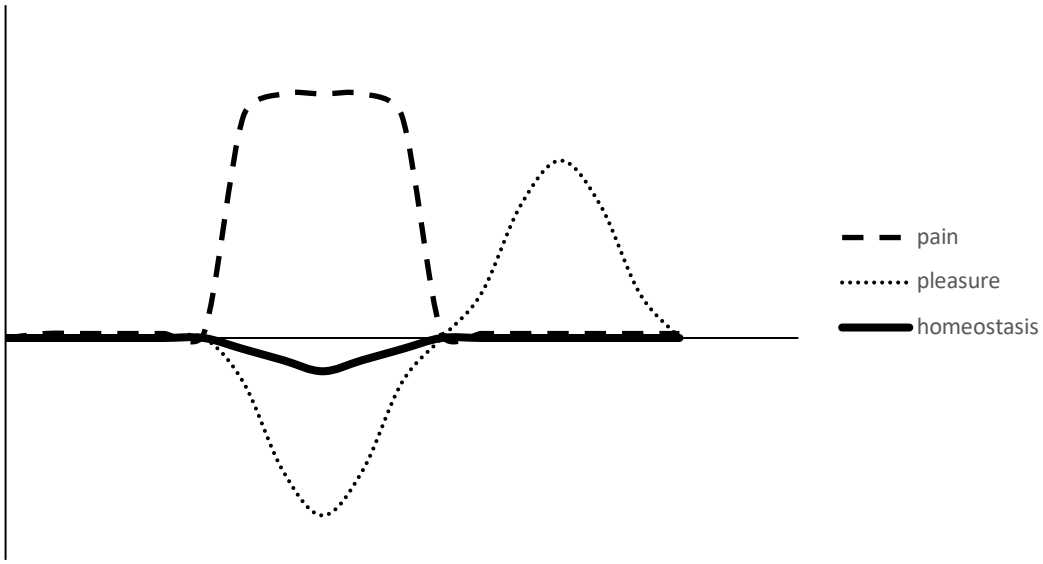


Figure 7. Graphical representation of the *opponent process theory based on theoretical data*. During pain onset, homeostasis is disrupted, and we observe decreased feelings of pleasure. Once pain is terminated, brain reward regions become significantly activated as a compensatory mechanism that helps prepare the return to homeostasis.

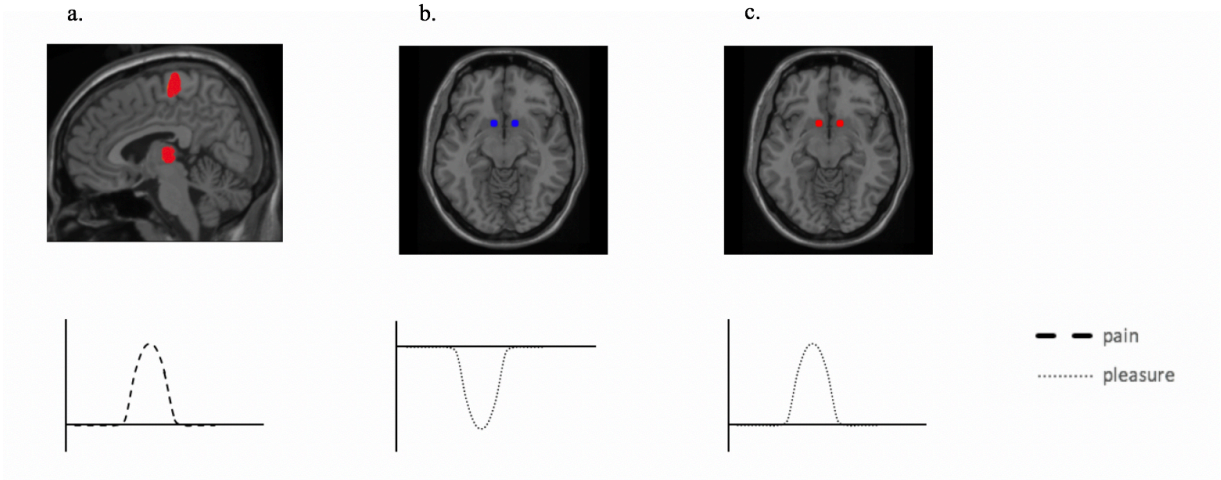


Figure 8. a. Activations in the thalamus and the primary somatosensory cortex during pain onset (theoretical data). b. Deactivation in the nucleus accumbens during pain onset (theoretical data). c. Activation of the nucleus accumbens during pain offset (theoretical data).

5.3.2 Methodological implications

Taking everything into consideration, our psychophysical and neurobiological findings have significant methodological implications. **Firstly**, the main important finding in study 1 was the lack of relationship between the ICPM phenomenon and pleasant pain relief. This is

imperative because a significative positive correlation would have implied that the analgesia measured by ICPM paradigms may be confounded by pleasant pain relief. **Secondly**, in study 2 we used a modified CPT (gel) which elicited potent pain intensity and pleasant pain relief as well as significant activations in key regions of the pain matrix, such as the insula, the thalamus and the paracentral lobule. Furthermore, these results are consistent with results obtained while using the original CPT (cold water bath), suggesting that the modified CPT was well suited for this experiment. In addition, the modified CPT eliminates the risk of water spillage, contrary to the original CPT. To our knowledge, only one other study used a similar protocol as us, a cold gel in which participants were asked to place their left hand (Lapotka et al., 2016). This study equally found activations in the insula and thalamus. However, unlike our study, they only investigated activations during pain onset, no control stimulus was administered (e.g. gel at room temperature) and no deactivations of the reward regions was found during pain onset. **Finally**, in both our studies, the CPT was administered twice, inside and outside the scanner, and we observed that the procedure had satisfactory test-retest reliability.

5.4 Limitations

While we found our results to be promising and useful in the field of pain research, there are some limitations we wish to address.

5.4.1 Participants

In both studies presented above, one of our main limitations is the small sample size. In total, 27 healthy individuals were recruited in study 1 and 26 healthy individuals were recruited in study 2. In study 1, we successfully showed a significant correlation between pain intensity

and pleasant pain relief. However, no correlation was found between ICPM efficacy and pleasant pain relief. Given the small sample size, this lack of correlation may be caused by a lack of statistical power.

In addition, in both study 1 and study 2, no correlation was found between depressive symptoms (measured by BDI-II) and pain intensity or pain unpleasantness. However, it is important to consider this result prudently as we cannot imply that there is no existing correlation between depression and clinical pain. A vast past literature has shown that chronic pain and depression tend to co-occur in patients (Velly & Mohit, 2018). However, in our studies, very few participants reported subclinical psychological symptoms in the BDI-II, SHPS or STAI. The lack of correlation between depression and pain intensity or pain unpleasantness may thus be caused by the lack of subclinical symptoms present in our population.

5.4.2 Stimuli

In study 1, pain intensity was measured by administering the original CPT (cold water bath) to participants' right arm. In opposition, a modified CPT (gel) was administered to participants' right foot in study 2. Although both studies induced significant pain, they used different types of stimuli (water vs gel) on different regions of the body (arm vs foot), which may cause an issue when comparing the results of the two studies. For instance, both the insula and the precuneus correlated with pain intensity measured during the scanning session, but the insula did not correlate with pain intensity measured in the psychophysical session. However, the posterior insula is involved in the processing of stimulus *location*. Therefore, the lack of correlation between the activation in the insula (caused by a painful stimulation to the foot) and pain intensity measured in the psychophysical session (caused by a painful stimulation to the

arm), may be due to the different body regions stimulated (K. B. Jensen et al., 2016; Wiech et al., 2010). Similarly, we found no correlation between the deactivation of the medial orbital frontal gyrus (induced by the modified CPT on the right foot) and pleasant pain relief or pain unpleasantness (induced by the original CPT on the right arm). This lack of correlation may once more be caused by the difference in stimuli type or region stimulated. Finally, the modified CPT also covered a smaller surface than the original CPT (the foot vs the whole arm) which may also cause differences in strength of activations, pain perception and pain relief.

5.4.3 Correlational analysis

In study 1, we found no significant relationship between ICPM efficacy and pleasant pain relief. However, this investigation was simply based on a correlational analysis; thus, we cannot fully rule out the possibility that ICPM may be influenced by pleasant pain relief. To fully eliminate the hypothetical relationship between ICPM efficacy and pleasant pain relief, one possible approach would be to cognitively manipulate one of the variables in question (ICPM or pleasant pain relief).

5.5 Recommendation for future studies

The interest in the field of pain research has continued to grow over several years. Yet, many aspects in regard to pain disorders still remain unknown. To our knowledge, pleasant pain relief has only been tested on healthy individuals. Though, investigating pleasant pain relief in patients with chronic pain may lead to important findings. Several affective comorbidities tend to co-occur with chronic pain, such as depression and anxiety. The relationship between chronic pain and mental health has most likely a bidirectional aetiology; chronic pain may cause

depression and vice versa. Either way, it is possible that the co-occurrence of depression in chronic pain would be associated with decreased pleasant pain relief. Therefore, more in-dept observations regarding the relationship between pleasant pain relief and chronic pain disorders are warranted.

Chapter 6. Conclusion

In the current memoir, two separate studies were conducted with the objective to deepen our understanding of the pain reward interaction using psychophysical and neurobiological measures.

In the **first study,** we investigated the interactions between pain and reward during pain offset which allowed us to explore 1) if pain offset induces pleasant pain relief and 2) if pleasant pain relief is a confounding factor in the ICPM system. To our knowledge, this study was the first to investigate the possible relationship between ICPM and pleasant pain relief. As we expected, pain offset induced pleasant pain relief. However, contrary to what we hypothesized, our results showed no relationship between the two paradigms, suggesting that ICPM may not be confounded by pleasant pain relief.

In our **second study**, we investigated cerebral activations/deactivations during pain onset, using a modified CPT (gel). This study found significant activations in the main regions of the pain matrix (e.g. the insula and the paracentral lobule) and significant deactivations in the medial orbital frontal gyrus during painful stimulation. These results illustrate the disruption in homeostasis in regard to the reward system during noxious stimulation, as shown by the deactivation of the medial orbital frontal gyrus. However, although we found a positive significant correlation between the regions of the pain matrix and pleasant pain relief, we found

no correlation between the medial orbital frontal gyrus (reward region) and pleasant pain relief. Still, our hypothesis regarding the deactivation of reward regions during pain onset was correct.

All though our studies revealed important findings in pain research, they presented certain limitations. For instance, although we investigated interesting relationships between psychophysical measures, these investigations were based on correlational analysis. Furthermore, the sample size of both studies was relatively small. A larger sample could have permitted us to investigate these relationships within a multivariate analysis. For instance, variables such as gender or psychological symptoms (e.g. depression or anxiety) may have an influence on the relationship between pain and pleasant pain relief. In addition, future studies should seek to replicate these studies in samples of chronic pain patients to determine if, similarly to healthy individuals, the termination of a noxious stimulus induces pleasant pain relief in chronic pain patients as well. The occurrence of anxiety and depression in some chronic pain patients may suggest that this population would have reduced pleasant pain relief at pain offset (Finucane, Dima, Ferreira, & Halvorsen, 2012; Sheng et al., 2017).

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