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Liste des abréviations

DLPFC: Dorsolateral Prefrontal Cortex

EMG: Electromyography

ERP: Event-Related Potential

IASP: International Association for the Study of Pain

ISI: Inter-stimulus Interval

ITI: Inter-trial Interval

NRS: Numerical Rating Scales

M: mean

NFR: Nociceptive Flexion Reflex

PANAS: Positive and Negative Affect Scale

RA: Response Accuracy

RT: Response Time

SEM: standard error of the mean

tDCS: Transcranial Direct Current Stimulation

WM: Working Memory

ACC: Anterior cingulate cortex:

RVM: Rostral ventromedial medulla

Amg: amygdala

Cd: caudate

Hi: hippocampus

Ins: insular cortex

LC: locus coeruleus

M1: primary motor cortex

NAc: nucleus accumbens

PAG: periacqueductal gray

PFC: prefrontal cortex

Pu: putamen

RVM: rostral ventral medulla

S1: primary somatosensory cortex

S2: secondary somatosensory cortex

SMA: supplementary motor area

Th: thalamus

TPJ: temporal-parietal junction

FEF: frontal eye field

IPS/SPL: intra parietal sulcus/superior parietal lobe

TPJ: temporo-parietal junction

VFC: ventral frontal cortex

IFG/MFG: inferior frontal gyrus/medial frontal gyrus

EEG: Electroencephalography

ERPs: electroencephalographic event-related potentials

fMRI: Functional magnetic resonance imaging

LEPs: laser-evoked potentials.

rTMS: repetitive transcranial magnetic stimulation

EMN: extrinsic mode network

DMN: default mode network

PPC: posterior parietal cortex

PMv: ventral premotor cortex

PCu/PCC: precuneus/posterior cingulate cortex

Mpfc: medial prefrontal cortex

Thal: thalamus

pACC: pregenual anterior cingulate cortex

vlPFC: ventrolateral prefrontal cortex

vStriatum: ventral striatum.

CSF: cerebrospinal fluid

WMC: Working memory capacity

To my Mom, Dad and my Brother,

Thank you for being there whenever I needed it, and even when I thought I did not need it.

Thank you for letting me find my way.

I owe it all to you.

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Chapter 1. Introduction

Chronic pain affects nearly 20% of the worldwide population and incurs an economic burden greater than cancer, heart disease, and HIV combined (Groenewald et al., 2014; Hogan et al., 2016; Moulin et al., 2002; Schopflocher et al., 2011). Pain, particularly in chronic cases, affects daily living activities including relations with others, sleep, general mobility, and sexual intimacy, and results in developing anxiety and depressive symptoms (Choiniere et al., 2010). Unfortunately, pain is often resistant to treatment and those therapies that do exist are associated with unwanted side-effects including medication dependence and overdose (Gomes et al., 2013; Green et al., 2010; Lynch, 2011). For example, prescription of opioid pain relievers for chronic pain has resulted in opioid addiction in two million people in the US. In addition to the risk of addiction and overdose, and the associated costs to the government, only one-fourth of chronic pain patients experience effective pain relief from opioids (Meyer et al., 2014).

As such, a critical need exists to develop alternative or supplemental treatment strategies including non-pharmacological approaches. In line with this, empirical evidence supports the possibility of the modulation of pain using cognitive-based approaches (Legrain et al., 2005b; Legrain et al., 2011a; Torta et al., 2017a; Van Damme et al., 2010b). For example, attention can facilitate or inhibit the processing of painful information (Legrain et al., 2009; Torta et al., 2017a; Van Damme et al., 2010b). Painful stimuli involuntarily grab our attention because our body prioritizes them in order to protect us from harmful stimuli (Van Damme et al., 2010b), but redirecting attention away from painful stimuli has been shown to inhibit pain (Legrain et al., 2005b). However, our attentional capacity is limited, and multiple sensory sources can overload this capacity via competing demands on the system (Legrain et al., 2009; Torta et al., 2017b; Van Damme et al., 2010b). Thus, it is critical to consider our ability to modulate the

attention given to painful stimuli as it represents one mechanism that could be leveraged in non-pharmacological interventions for chronic pain.

To have effective attentional control over pain, simply disengaging attention from the pain stimuli is not enough; it is also necessary to maintain attention towards relevant information (Legrain et al., 2005a; Legrain et al., 2013; Legrain et al., 2009). Many studies have demonstrated that it is working memory (WM) that allows us to prioritize the maintenance of relevant information in the face of task-irrelevant information (Baddeley, 2012; Baddeley et al., 1974; D'Esposito et al., 2015; de Fockert, 2013; Legrain et al., 2011a). Given that WM performance is impaired in patients with chronic pain and in normally aging populations (Baker et al., 2016; Berryman et al., 2014; De Beni et al., 2004; Gazzaley et al., 2005b; Sambataro et al., 2010), it is possible that their ability to exert attentional control over pain may be reduced as a result of their impaired WM. At the same time, this raises the possibility that their attentional regulation over pain can be enhanced by improving their WM performance. Although no therapeutic intervention has been suggested to reduce pain by improving WM performance yet, Transcranial Direct Current Stimulation (tDCS) could be an appropriate tool to fill this gap due to its ability to modulate brain activity related to both WM performance and pain perception (Andrews et al., 2011b; Boggio et al., 2006a; Hill et al., 2016; Jo et al., 2009; Mariano et al., 2016; Mylius et al., 2012b; Park et al., 2014; Wolkenstein et al., 2013) .

My doctoral work focuses on the effect of WM engagement, and the improvement of WM engagement by applying tDCS, on pain inhibition in healthy young and old adults. First, I will overview current understanding of pain definition, pain processes, and pain pathways.

Then, I will summarize important cognitive concepts related to attentional modulation of pain, and present theoretical frameworks that try to explain the relationship between attention and pain. These theoretical frameworks will highlight the critical role of cognitive, affective, and motivational factors in explaining the trade-off between attention and pain. In addition, these theoretical frameworks will provide an appropriate background against which to explain "the neurocognitive model of attention to pain", which is the main model used in our projects. The most important recent empirical evidence concerning experimental studies of pain and attention in healthy young and old individuals will be presented. Next, the role of the dorsolateral prefrontal cortex in WM and pain perception in both healthy young and old adults will be reviewed. I will then review the reasons for which we chose healthy older adults for this project. I will also summarize the effect of tDCS on WM performance and pain perception of both groups. Finally, this chapter will end with an explanation of our motivation to conduct these projects, while also clarifying our aims and hypotheses.

1. Pain physiology

Pain is a subjective, complex, biopsychosocial experience. It arises from multiple interactions in the body and brain involving neuroanatomic, neurochemical, cognitive, and affective processes (Garland, 2012). "The International Association for the Study of Pain (IASP)" has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"(Merskey, 1994.). Therefore, the critical components of pain can be listed as sensory, affective, and cognitive

(Garland, 2012). To clarify how pain is perceived, the following (Section 1.1) will provide a summary of the pain physiology and the major pain pathways.

Transmission of nociceptive information to the brain is called nociception, as distinct from the subjective pain experience (Brodal, 2010; Garland, 2012). According to the early model of nociception, the transduction of noxious stimuli followed by the transmission of these signals would lead to the subjective perception of the painful stimuli. However, modulation of nociception can reduce or enhance our perception of pain at all levels of this system (Garland, 2012; McMahon et al., 2013; Serpell, 2008a). This section has been included to explain the physiology of pain, under the following headline of pain processing pathways, which includes transduction, transmission (including ascending pathways of pain) and perception of pain. Further modulation of nociception will be clarified by explaining the descending pain modulatory system.

1.1 Pain processing pathways

The four basic processes involved in nociception and pain can be listed as follows: transduction; transmission; perception; modulation of pain (Garland, 2012; Serpell, 2008a).

The first step is transduction, which occurs when pain receptors in peripheral tissues are activated by noxious stimuli (Garland, 2012; Serpell, 2008b). These pain receptors are the terminal ends of specific neurons called nociceptors. Pain receptors or nociceptors are spread throughout the body (skin, viscera, muscles, joints, meninges) and respond to intense

mechanical stimulation (e.g. stretching, cutting, pressuring or pinching), thermal stimulation (both cold and heat), or chemical stimulation (e.g. toxic substances, inflammatory mediators, and infection). These receptors activate primary afferent neurons, which terminate in the dorsal horn of the spinal cord. Different types of nociceptors transmit specific sensory information through specific sensory fibers (Brodal, 2010; Garland, 2012). For example, Aδ fibers, which are lightly myelinated, transfer mechanical and thermal signals. They are responsible for fast, sharp pain and the initial reflex response to acute pain. C fibers, which are unmyelinated, are slower and transfer chemical, mechanical, and thermal signals leading to burning, aching or itching pain (Garland, 2012; Loeser et al., 1999). To summarize, during the transduction step, pain receptors and sensory fibers (e.g. Aδ and C fibers) are activated by noxious stimuli (e.g. mechanical, thermal, or chemical stimulation) (Garland, 2012; McMahon et al., 2013; Serpell, 2008a).

The second step after transduction is transmission, wherein information about noxious stimuli is sent along neural pathways from the peripheral division of the nervous system to the central and autonomic nervous systems (McMahon et al., 2013; Serpell, 2008a). The three stages of the transmission process are: 1) transmission of signals from the nociceptors to the dorsal horn of the spinal cord; 2) transmission of signals from the spinal cord to the brainstem and thalamic nuclei; 3) transmission of signals from the thalamus to the cortex (McMahon et al., 2013; Serpell, 2008b). To clarify, signals from C and Aδ fibers, which terminate in the dorsal horn of the spinal cord, are then transmitted from the spinal cord to the brainstem and thalamus, and afterwards to multiple cortical and subcortical regions (Garland, 2012; McMahon et al., 2013). This transmission occurs through two main nociceptive ascending pathways: the

spinothalamic and the spinoreticular pathways (Garland, 2012; Sherman et al., 1996). The spinothalamic tract is initiated from fibers in the dorsal horn and ascends both anteriorly and laterally in the white matter of the spinal cord. The lateral spinothalamic tract ascends directly to the thalamus (including the ventral posterolateral nucleus of the thalamus) and is associated with discrimination of sensory features of pain perception (Willis et al., 1997). The medial spinothalamic tract ascends to the periaqueductal grey matter (PAG), hypothalamus, and reticular system in the midbrain, from which it continues to the medial thalamus (Willis et al., 1997). The medial spinothalamic tract is associated with moderating emotionally unpleasant components of pain. Both spinothalamic tracts send information to areas of the cerebral cortex (Garland, 2012; Serpell, 2008b). The spinoreticular tract originates in the dorsal horn of the spinal cord, and ascends along with the spinothalamic tracts in the anterolatreal funiculus, to terminate in the reticular formation of the medulla and pons of the brainstem. From various reticular formation nuclei, its information is then relayed to the thalamus, hypothalamus, and multiple areas of the cerebral cortex (Serpell, 2008b). The spinoreticular system is also associated with an unpleasant emotional experience of pain (Serpell, 2008b; Willis et al., 1997). Transmission of nociceptive signals often leads to pain perception, but this transmission is distinct from the pain experience (McMahon et al., 2013; Serpell, 2008b; Tracey et al., 2007; Willis et al., 1997). To sum up, during the nociception process, information about noxious stimuli is transmitted from the spinal cord to the cerebral cortex and other subcortical areas via nociceptive ascending pathways (Garland, 2012; McMahon et al., 2013; Serpell, 2008a).

The third step is pain perception, which usually arises from the transmission of nociceptive signals to the brain, and in which pain is perceived as a multidimensional

phenomenon (Garland, 2012; Serpell, 2008a) . The brain network underlying pain processing, known as the "pain matrix" historically, had distinct sensory-discriminative and cognitive-affective systems (see **Figure 1**) (Martucci et al., 2018; McMahon et al., 2013; Melzack, 2005; Wiech, 2016; Wiech et al., 2008a). The sensory-discriminative system was believed to be responsible for the processing of nociceptive input (e.g. intensity, localization, and quality), particularly from large afferent fibers (A delta), from thermal and high-threshold mechanical receptors (Bishop et al., 1958; Garland, 2012). This system would involve regions such as the lateral thalamus and primary and secondary somatosensory cortices (S1 and S2), while the cognitive-affective system was associated with processing affective/emotional aspects of pain and involved the anterior insula and anterior cingulate cortex (ACC) (McMahon et al., 2013; Serpell, 2008a; Tracey et al., 2007). However, this historical pain matrix model appeared to be oversimplified. For example, evidence suggests that regions associated with the sensory-discriminative aspects of pain processing can also be affected by cognitive processes (Wiech, 2016). Pain perception is a complex process that can arise without painful stimuli (Garland, 2012; Tracey, 2017; Wiech, 2016). Additionally, nociceptive processes can occur without leading to a subjective pain experience, due to complex and non-linear interactions between nociceptive processes and pain perception (Garland, 2012; Mano et al., 2015; Serpell, 2008a; Tracey et al., 2007; Wiech, 2016).

The last step is pain modulation. The brain modulates activity in the dorsal horn of the spinal cord via the descending pain modulatory pathway, which can inhibit and disinhibit nociceptive signal transmission (Bantick et al., 2002; McMahon et al., 2013; Tracey et al., 2007; Wiech, 2016; Wiech et al., 2014; Wiech et al., 2008a). There are various cortical and subcortical

structures involved in this process of top-down modulation of pain (McMahon et al., 2013; Serpell, 2008a). According to multiple neuroimaging studies, these regions include: the prefrontal cortex, ACC, insula, dorsolateral prefrontal cortex (DLPFC), amygdala, hypothalamus, periacqueductal gray (PAG), and the rostral ventromedial medulla (RVM) (see **Figure 1**) (Legrain et al., 2009; Martucci et al., 2018; McMahon et al., 2013; Seminowicz et al., 2007d; Seminowicz et al., 2017; Serpell, 2008a). For example, activation of the DLPFC, insula, and ACC, which are mainly related to the affective and cognitive aspects of pain, have been shown to modulate pain perception (Tracey et al., 2007). Additionally, studies have found that this top-down influence can affect nociceptive processing at an early stage by modifying responses in the spinal dorsal horn (Eippert et al., 2009b; Roy et al., 2011; Wiech, 2016). To summarize, investigations of the descending pain modulatory system have introduced how cognitive factors might affect pain perception.

Transduction, transmission, and modulation are neural processes and can be studied using methods that involve direct observation of electrical activity. However, pain perception cannot be directly and objectively measured because the pain experience is subjective, despite its neural basis. For example, we can measure neuronal transmission, but we cannot conclude that a person feels pain; we require indirect evidence such as self-report (Serpell, 2008a).

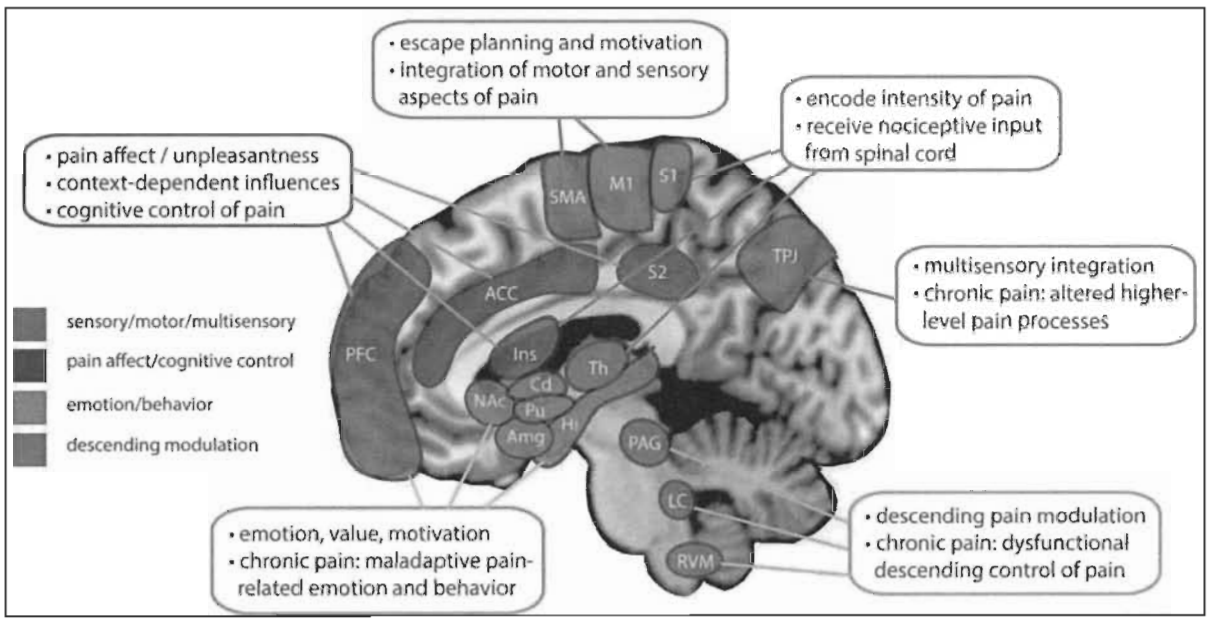

Figure 1. "Brain areas that are part of the pain matrix"

"This figure is displaying the main supraspinal regions and their roles in pain processing. Multiple cortical and subcortical structures are involved in various primary roles and aspects of the pain experience: ACC = anterior cingulate cortex; Amg = amygdala; Cd = caudate; Hi = hippocampus; Ins = insular cortex; LC = locus coeruleus; M1 = primary motor cortex; NAc = nucleus accumbens; PAG = periacqueductal gray; PFC = prefrontal cortex; Pu = putamen; RVM = rostral ventral medulla; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SMA = supplementary motor area; Th = thalamus; TPJ = temporal-parietal junction. The regions are all projected on a mid-sagittal section of the brain." Figure is taken from (Martucci et al., 2018).

This section has reviewed the four critical aspects of the pain experience, namely transduction, transmission, pain perception, and modulation (Garland, 2012; Serpell, 2008a). In transduction, noxious stimuli activate nerve endings. In transmission, the signal is sent from the

tissue injury location (or stimulated tissue without lesion) to the brain regions related to perception (Garland, 2012; McMahon et al., 2013; Serpell, 2008a). Different types of nociceptors initiate different pathways of nociceptive transmission, which contribute to a complex signaling process (Garland, 2012; McMahon et al., 2013; Serpell, 2008a). The information is sent via ascending pathways through the spinal cord to the brain. The ascending spinal pathways involve both the thalamus and brainstem nuclei, and project higher in the brain via many cortical pathways (Brodal, 2010; Garland, 2012; Willis et al., 1997). Signals from the pain matrix (various cortical and subcortical regions) can regulate nociception and pain perception through descending pathways (Garland, 2012; McMahon et al., 2013; Serpell, 2008a; Tracey et al., 2007). The nociception process does not inevitably result in pain perception; pain results from the activity of integrated brain networks. Indeed, information about pain gets more integrated with other information as it ascends to the brain. Thus nociceptive input can be modified based on this integration of information, which gives a possible mechanism for the influence of cognitive factors including attention and WM (Garland, 2012; Legrain et al., 2009; McMahon et al., 2013; Tracey et al., 2007; Wiech, 2016; Wiech et al., 2008b).

To understand the whole picture of pain perception and pain modulation, it is necessary to consider the effect of other important factors. My doctoral work is focused on the effect of cognitive factors, primarily attention and working memory, in pain modulation. In the next section, I will discuss important cognitive concepts in the field of attentional modulation of pain.

2. Cognitive concepts related to pain modulation

As previously mentioned, cognitive, emotional, and psychophysiological factors modulate pain and the nociceptive process. Empirical evidence illustrates the role of cognitive functions, mainly attention, in pain processing. The main model utilized in my doctoral work is the "neurocognitive model of attention to pain" (Legrain et al., 2009) (it will be explained in Section 3.4). This theory explains how bottom-up capture of attention and top-down modulation interact with WM to modulate pain perception. The "neurocognitive model of attention to pain" was developed based on previous models including the model of "limited attentional capacity/resource theory" (McCaul et al., 1985) (it will be explained in Section 3.1), "the cognitive-affective model of the disturbing effect of pain" (Eccleston et al., 1999a) (it will be explained in Section 3.2), and the "motivational account of attention to pain" (Van Damme et al., 2010b) that explain how pain interacts with attention and vice versa (it will be explained in Section 3.3).

Before explaining "the neurocognitive model of attention to pain" and other related models, it is necessary to introduce separate, fundamental concepts of those theories including selective attention (it will be explained in Section 2.1), "the attention system of the human brain" (it will be explained in Section 2.2), bottom-up vs. top-down attentional processes (it will be explained in Section 2.3), and working memory (it will be explained in Section 2.4). In addition, different types of attentional processes might modify pain and nociceptive processes by affecting different cortical mechanisms (Raz et al., 2006; Torta et al., 2017a). The next section

reviews some fundamental concepts and models of attention to clarify how and why some stimuli can be selected while others are ignored.

2.1 Selective attention

William James defined the concept of attention as choosing one stimulus out of several for conscious processing (James, 1890). Regarding this view, selective attention – one of the terms most commonly used to refer to attention – is considered a filter that prioritizes the processing of relevant information (Broadbent, 1958; Hommel, 2010; James, 1890). Selecting relevant information is critical for our limited cognitive capacity because it is impossible to process all available information simultaneously (Broadbent, 1958; Kahneman et al., 1984). In addition to James' view, Alan Allport also defined attention as a system that can prioritize and select the most relevant action (Allport, 1989). He considered two different functions of an efficient attentional system: first, attention protects the ongoing behavior (current goals) from distractors; second, ongoing behavior can be disturbed when critical demands (such as threats) appear unpredictably (Allport, 1989; Norman et al., 1986; Van Damme et al., 2010b). Maintaining the balance between these functions is required for survival; shifting to new information too frequently can lead to chaotic behavior, while ignoring environmental threats is potentially hazardous (Allport, 1989; Fishbach, 2007; Van Damme et al., 2010b). For example, in the context of a painful situation, selecting painful stimuli can interrupt ongoing actions in order to prioritize escape or defensive behavior (Torta et al., 2017a; Van Damme et al., 2010b; Van Ryckeghem et al., 2018). In summary, according to these two views selective attention prioritizes relevant information and selects the most appropriate action to achieve ongoing goals.

2.2 The attention system of the human brain

Posner and Petersen proposed three distinct processes of attentional system, along with three related brain areas and networks (Petersen et al., 2012; Posner, 1989; Posner, 2016). The first stage is referred to as an alerting process that makes us aware of the overall sensory feeling our attention being captured and that activates the right hemisphere, particularly the thalamic, frontal, and parietal areas (Fan et al., 2005; Fan et al., 2002; Petersen et al., 2012; Posner et al., 1990). The second stage is referred to an orienting process that selects the modality or location of the sensory input for further processing (Petersen et al., 2012; Posner et al., 1990). For example, if we cue the location of a target, it will orient our attention to this location. Orientation can occur either overtly, with eye movement, or covertly, without eye movement (Posner, 2016). The orienting network activates the parietal and frontal areas: activation of the superior parietal lobe is associated with following cues; activation of the temporal-parietal junction is related to the disengagement of attention and guidance to a new location; and activation of the frontal areas is associated with quick attentional control (Ollinger et al., 2000; Petersen et al., 2012; Posner, 2016; Posner et al., 1990). The third attention stage is called the executive attention process, which detects relevant targets and resolves the conflict between choosing relevant stimuli and ignoring irrelevant stimuli (Petersen et al., 2012; Posner et al., 1990; Torta et al., 2017a). Neuroimaging studies indicate that monitoring conflict activates the dorsal ACC while resolving a conflict activates the DLPFC (Bush et al., 2000; Fan et al., 2005; Posner, 2016). The concept of executive attention in the Posner and Petersen model overlaps with executive functions (i.e. attentional control, cognitive inhibition, and WM processes are involved in executive functions, which implies that these cognitive processes are essential for cognitive

control and achievement of selected goals) (Chan et al., 2008; Diamond, 2013). In addition, executive attention clearly overlaps with the concept of selective attention (i.e. prioritizes relevant information and selects the best action, as mentioned previously) (Torta et al., 2017a). However, in the Petersen and Posner model executive attention is considered a process that helps us to maintain cognitive control mainly over irrelevant information. In addition, in this model, each stage is associated with activity in specific brain networks (Dosenbach et al., 2007; Dosenbach et al., 2006; Posner et al., 2007; Torta et al., 2017a) (see **Figure 2**).

To summarize, Posner and Petersen proposed three distinct stages of attention in the human brain including alerting stage, which is the ability to be aware of the upcoming stimulus, (2) orienting attention stage, which implies attentional direction to a particular sensory stimuli and selecting it among several ones, and (Riley et al.) executive attention stage, which is associated with behavioral control in conflict situations (Petersen et al., 2012; Posner, 2016; Posner et al., 1990). The executive attention concept is essential to pain research because allocating attention to non-pain-related cognitive tasks can inhibit attention to painful stimuli (Buhle et al., 2010; Legrain et al., 2011a; Legrain et al., 2011b; Legrain, 2011b; Seminowicz et al., 2007b; Torta et al., 2017a; Van Damme et al., 2010a).

The concept of selective attention is a broad concept, which overlaps with all three of the processes in the Posner and Petersen model. However, selective attention is not a unitary process (Torta et al., 2017a). For example, pain and brain responses to nociceptive stimuli can be modulated by different attentional processes (e.g. orienting or executive attention).

Therefore, considering selective attention as a unitary process might result in over-generalized conclusions (Raz et al., 2006; Torta et al., 2017a).

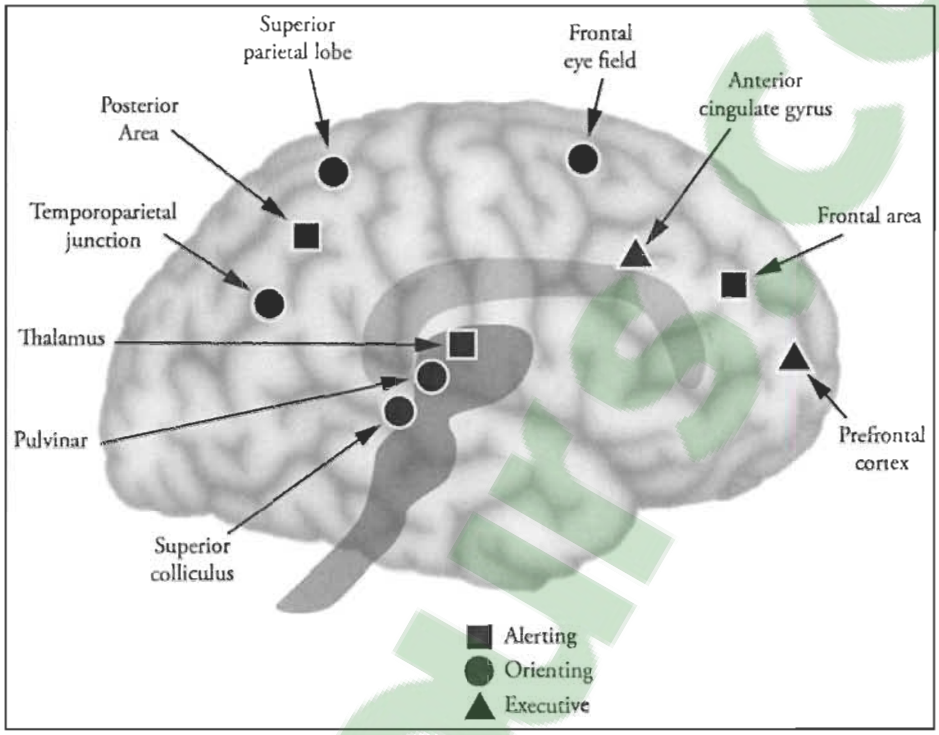

Figure 2. Anatomy of three attentional networks

Figure is taken from (Posner et al., 2007).

The following section provides a brief explanation of one of the most critical attentional processes – the distinction between bottom-up and top-down processes. In the next paragraphs, I will also attempt highlight the parallels between the bottom-up and top-down processes in Posner and Petersen's model and the dorsal/ventral attentional networks proposed by Corbetta and Schulman (Corbetta et al., 2008; Corbetta et al., 2002; Petersen et al., 2012; Posner, 2016).

2.3 Bottom-up vs top-down attentional processes

Salient stimuli (i.e. too strong to be ignored) can attract attention automatically and involuntarily (Theeuwes, 1991). This process is called "bottom-up" or "stimulus-driven" capture of attention, or exogenous attention. Bottom-up attentional processing results in the detection of changes in ongoing sensory stimuli – detecting differences between a recent event and new sensory stimulus (Egeth et al., 1997; Knudsen, 2007; Yantis, 2008; Yantis et al., 1990). Bottom-up attentional processes are the opposite of top-down processes – endogenous attention processes that often involve the voluntary capture of attention. Top-down processes can direct us to, and focus us on, goal-relevant information, while bottom-up processes can re-orient attention to salient stimuli (Escera et al., 2014; Legrain et al., 2009; Näätänen, 2011; Polich, 2007; Torta et al., 2017a). In order to connect bottom-up and top-down processes to the previous section, both of these processes are integrated into the orienting network of the Posner and Petersen model in which top-down processes select task-relevant information and rely on internal task goals, while bottom-up processes select salient stimuli based on physical distinctiveness. In summary, bottom-up and top-down processes work in harmony (Torta et al., 2017a). For example, imagine a runner who has trained for a year to participate in a marathon. On the day of the marathon she starts the race with the goal to finish it (top-down processes). Suddenly while running, she steps on a nail that pierces her shoe (salient stimuli) and she feels a sharp pain in her foot. Her attention automatically shifts to the pain, so she stops running for a moment and forgets her goal to finish the marathon (bottom-up processes). After pulling out the nail, she continues running (goal-directed behavior). Although she still has pain in her foot, she forgets it and focuses once again on finishing the marathon (top-down processes).

These two systems activate two distinctive brain networks (Petersen et al., 2012; Posner, 2016). The first is a ventral attentional network that is associated with bottom-up processes and the detection of salient stimuli, and includes the temporo-parietal and inferior frontal cortices. The second is the dorsal attentional network, which is related to top-down processes and active selection of relevant information, and which includes the intraparietal cortex and the superior frontal cortex (Corbetta et al., 2002; Petersen et al., 2012; Posner, 2016). These two networks interact with each other (Corbetta et al., 2002). For example, performing a cognitive task such as a Stroop task can suppress the activity of the ventral parietal network, while presenting salient stimuli (such as painful stimuli) might interrupt the activity of the dorsal parietal network (Corbetta et al., 2008; Fougnie, 2009; Kiyonaga et al., 2013; Legrain et al., 2009; Stroop, 1992) (see **Figure 3**).

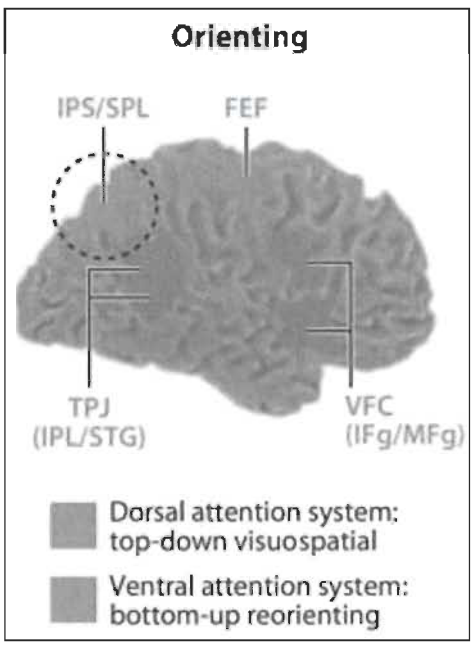

Figure 3. « Anatomy of the ventral and dorsal attention networks »

"FEF = frontal eye field, IPS/SPL = intra parietal sulcus/superior parietal lobe, TPJ = temporo-parietal junction, VFC = ventral frontal cortex, IFG/MFG = inferior frontal gyrus/medial frontal gyrus. Figure is taken from" (Petersen et al., 2012)

Thus far, this section has reviewed several concepts of attention– including selective attention, the orienting of attention, and bottom-up vs. top-down attentional processes. However, attention is not the only component in cognition (Awh et al., 2012). The following section (2.4) will consider another cognitive factor – working memory (WM) – and clarify how attention and WM interact.

2.4 Working memory

WM maintains information active for a short period of time and is comprised of three distinct processes: the encoding, storing, and manipulation of information (Baddeley, 2003; Postle, 2006; Woodman et al., 2005). WM manipulates stored information without perceptual input (e.g. visual information is maintained in visual WM) (Baddeley, 2012). WM is as a component of executive function and as such it is involved in all complex cognitive processes such as reasoning, decision-making, and the top-down attention processes (Diamond, 2013).

The idea of WM evolved from the concept of short-term memory and the two terms are sometimes used interchangeably (Fuster, 1997). However, some theories have clarified that short-term memory is related exclusively to the storage of information while WM includes both storage and manipulation of information (Baddeley, 2003; Baddeley, 2012; Miyake et al., 1999).

Several WM models have tried to describe the process of working memory in terms of cognitive mechanisms and their corresponding anatomical structures (Miyake et al., 1999). Here, I will summarize the most influential model – the multicomponent model of WM of Baddeley and Hitch (Baddeley, 2003; Baddeley et al., 1974).

This model includes four central mechanisms: the phonological loop, the visuospatial sketchpad loop, the central executive, and the episodic buffer (Baddeley, 2012; Baddeley et al., 1974). The phonological loop stores sound (phonological information). Visual and spatial information about stimuli such as shape, color, and location are maintained in the visuospatial sketchpad loop. The central executive controls information processing in the phonological loop and visuospatial sketchpad loops: it updates and manipulates information, guides attention to targets, inhibits the processing of irrelevant information, and controls cognitive processes during multitasking. The episodic buffer – which was added recently as the fourth element of the model – maintains multi-modal representations of information like semantic information. Additionally, it integrates information from different loops to form a coherent whole, combines information, and links WM to long-term memory (Baddeley, 2003; Baddeley, 2012; Baddeley et al., 1974). An example of WM mechanisms is illustrated in the n-back task, which is designed to assess WM performance (Jaeggi et al., 2010; Kirchner, 1958; Mackworth, 1959). It consists of a list of visual or auditory stimuli in which participants have to indicate for each stimulus whether it is a correct match with the Nth stimulus presented before. In the n-back task, visual or auditory stimuli are stored in the phonological loop or visuospatial sketchpad loop while selection of the correct answer depends on the central executive function that is responsible for updating

information and inhibiting the processing of irrelevant information (Jaeggi et al., 2010; Kane et al., 2007).

In the multi-component model of Baddeley and Hitch, WM and attention are connected via the central executive system (Baddeley, 2003; Baddeley, 2012; Baddeley et al., 1974; Fougnie, 2009). The central executive concept overlaps with the concept of executive attention from the Posner and Petersen model in the previous section (Fougnie et al., 2009; Petersen et al., 2012; Posner, 2016; Wager et al., 2003). Baddeley proposed that the central executive is responsible for controlling attentional processes instead of being simply a memory store, making it different from the phonological and the visuospatial sketchpad loops that just store information. Indeed, the central executive, similarly to executive attention, selects relevant stimuli and ignores irrelevant stimuli (Awh et al., 2006; Baddeley, 2003; Baddeley, 2012; Baddeley et al., 1974; Engle et al., 1999; Fougnie, 2009; Heitz et al., 2007).

Engle and colleagues have proposed that an executive attention control mechanism can affect WM capacity and in turn WM performance (Conway et al., 2003; Engle et al., 1999). This executive attention control mechanism is mediated by activity of the prefrontal cortex (including DLPFC), where goal-relevant information can be actively maintained even in the presence of distractors (Engle et al., 1999; Klencklen et al., 2017). Likewise, Unsworth and colleagues have proposed that individual differences in WM performance can be associated with differences in three different mechanisms: 1) attentional control, which is the ability to maintain relevant information despite the presence of distractions; 2) the number of items that can be kept in WM capacity; or 3) the ability to retrieve information from long-term memory and bring it into the

focus of attention (Unsworth et al., 2014). These models attempt to explain the WM concept and individual differences in WM performance (Klencklen et al., 2017). However, it is difficult to determine which of the many mechanisms and components proposed to make up WM are responsible for individual differences and age-related changes in WM performance.

Thus far, the previous section has reviewed selective attention, the orienting of attention, bottom-up vs. top-down attentional processes, and WM processes. As discussed previously, all of these attentional concepts have overlap with each other. However, attentional research has not yet developed a unified model. In addition, none of these definitions are intended to be specific for pain. However, these concepts provide a basis for understanding theoretical frameworks of pain in which these definitions are frequently used (Torta et al., 2017a). In (Section 3), I will explain some of the major theoretical frameworks and empirical evidence that suggest a bidirectional interaction between pain and attention.

3. Theoretical explanations of the interaction between pain and attention

In the sections that follow, I will briefly summarize some of the main theoretical frameworks that aim to explain the interplay between attention and pain, including limited attentional capacity theories (McCaul et al., 1985) (Section 3.1), a cognitive-affective model of the interruptive function of pain (Eccleston et al., 1999b) (Section 3.2), and a motivational account of attention to pain (Van Damme et al., 2010b) (Section 3.3). In addition, Section 3.3 will review the empirical evidence relevant to these theoretical frameworks. As mentioned

previously, a neurocognitive model of attention to pain –the main model for my doctoral work – builds on these theoretical frameworks. Therefore, explaining them will help to understand better the neurocognitive model of attention to pain and to clarify how the attentional concepts and models are integrated into this model (Section 3.4). In addition, I will provide an overview of the empirical evidence relevant to this model (Section 3.4).

3.1 Limited attentional capacity theories

According to limited attentional capacity theories, consciously processing all available information would overload the cognitive system. For example, the Kahneman's single-capacity model proposes that there is limited attentional capacity, such that allocating attention to one stimulus results in reduced attention to other potential targets (Kahneman, 1973; Kahneman et al., 1984). Similarly, the bottleneck theory suggests that there are filters to control attentional contents during processing of stimuli, such that only salient stimuli can be perceived (Broadbent, 1958; Tabry, 2016; Van Ryckeghem et al., 2018).

Regarding the interaction between limited attentional capacity and pain, painful stimuli involuntarily grab our attention because our body prioritizes them in order to protect us from harmful stimuli (Downar et al., 2002; Downar et al., 2003; Van Damme et al., 2010b), while diverting attention has been shown to inhibit pain (Legrain et al., 2005a; Legrain et al., 2013; Legrain, 2011a). However, as our attentional capacity is limited, multiple sensory sources overload our capacity and result in system competition (Duncan, 1980; Legrain et al., 2009; McCaul et al., 1985). Thus, it is important to understand our ability to modulate the attention

given to painful stimuli. For example, performing a cognitively demanding task that requires allocation of more attentional resources to task-relevant information leads to less available resources to process other information. In one study, Legrain and colleagues presented a simple cognitive task (0-back) during which participants indicated the color of the current stimulus directly after its presentation, and a difficult cognitive task (1-back) during which they indicated the stimulus presented one trial back, during which painful stimuli were also presented. They demonstrated that perceived pain decreased while participants performed the 1-back task, compared to the 0-back task, suggesting an inhibitory effect of more demanding cognitive tasks on pain perception (Legrain et al., 2011a; Legrain et al., 2013).

3.2 Cognitive-affective model of the interruptive function of pain

The cognitive-affective model focuses on the interaction between painful stimuli and pain perception and how it is affected by a variety of cognitive and affective factors (Eccleston et al., 1999a). This model proposes that pain, which is a threatening signal, interrupts ongoing behavior in order to protect ourselves by prompting us to manage the pain (Bar-Haim et al., 2007; Eccleston et al., 1999a; Van Damme et al., 2010b). Similar to Allport's model of attention, ongoing behavior can be disturbed when critical demands such as threats appear unpredictably (as discussed in Section 2.1) (Allport, 1989; Eccleston et al., 1999a; Van Damme et al., 2010b). According to a cognitive-affective model of the interruptive function of pain, various cognitive and affective factors including saliency and novelty of stimuli, as well as individual characteristics such as pain catastrophizing and hypervigilance, modulate attention to pain

(Eccleston et al., 1999a; Legrain et al., 2009; Torta et al., 2017a; Van Ryckeghem et al., 2018). The following is a brief description of these influential cognitive and affective factors.

Due to their distinctive physical features compared to other sensory stimuli, salient sensory stimuli, can involuntarily capture attention (Egeth et al., 1997; Knudsen, 2007; Legrain et al., 2013; Yantis et al., 1990). We can detect salient stimuli in our environment due to specific neurons that are sensitive to contrasts and changes between stimuli (Desimone et al., 1995; Itti et al., 2001; Legrain, 2011b). Salience detectors react more strongly to those contrasts and changes, resulting in greater cortical resources allocated to salient sensory input (Downar et al., 2002; Eccleston et al., 1999b; Kucyi et al., 2012; Legrain et al., 2013; Legrain, 2011b; Seeley et al., 2007). One feature that can make stimuli salient is novelty, which describes stimuli presented for the first time or presented infrequently (Eccleston et al., 1999a; Legrain et al., 2013; Legrain, 2012; Norman et al., 1986). Novel stimuli can capture attention and interrupt ongoing cognitive activities (Crombez et al., 1997; Eccleston et al., 1999a; Escera et al., 2007; Näätänen, 2011). This capture of attention occurs by involuntary selection (a bottom-up process) (Legrain, 2012; Torta et al., 2017a). In regards to nociceptive processing, one study found that participant performance was decreased in an auditory discrimination task in which random painful stimuli were presented. The results indicated that attention was directed from the auditory target to the painful distractor irrelevant to the task goal, indicating involuntary capture of attention by salient and novel painful stimuli (Crombez et al., 1994; Eccleston et al., 1999b). Studies have shown that the cortical response to nociceptive stimuli is more sensitive to their novelty rather than their intensity. For example, in one study, the authors applied two kinds of nociceptive stimuli with the same intensity. Some of the stimuli were novel and unexpected, as

they were presented irregularly, while the others were presented regularly. The findings indicated that the novel stimuli provoked larger amplitude event-related brain potentials (ERPs) compared to the regularly presented stimuli (Legrain et al., 2003). In another study, participants had to perform a visual task in which some of the stimuli were followed by novel nociceptive stimuli that were task-irrelevant, compared to a condition in which the nociceptive stimuli were not novel. The results showed that the novel nociceptive stimuli could disturb performance on the visual task. In summary, saliency and novelty of painful stimuli are factors that increase the threat value of pain and contribute to attentional engagement (Eccleston et al., 1999a; Gisèle, 2015; Legrain, 2012; Van Ryckeghem et al., 2018).

Another important factor that can modify pain perception is pain catastrophizing, which is the tendency to predict catastrophic outcomes from pain, ruminate about pain, and feel helpless about pain (Eccleston et al., 1999b; Sullivan et al., 1995). Catastrophizing increases attention to painful stimuli and leads to perceiving pain more intensely (Crombez et al., 1998; Dillmann et al., 2000; Eccleston et al., 1999a; Keogh et al., 2001; Sullivan et al., 1995). For example, one study used a tone-discrimination task with several short durations and low-intensity electrocutaneous stimuli, while participants were informed that they would experience high-intensity pain. At the beginning of the experiment, participants were categorized as either high or low pain catastrophizers by applying the Pain Catastrophizing Scale (Crombez et al., 1998; Sullivan et al., 1995). The findings revealed that the attentional disruption by electrocutaneous stimuli and pain perception was increased for the high pain catastrophizers (Crombez et al., 1998; Eccleston et al., 1999a; Torta et al., 2017a).

Vigilance – amplified awareness of threat – is related to high levels of fear, which can worsen pain perception (Eccleston et al., 1999a; Eysenck, 1992). For example, chronic pain patients are typically hypervigilant to pain and their bodily sensations. In parallel, the fear-avoidance model also supports the idea that fearful patients show hypervigilance and pay more attention to threat signals, leading to avoidance behavior, increased disability, and the development of chronic conditions (Vlaeyen et al., 2000). Some patients with fibromyalgia or chronic low back pain maintain and amplify bodily sensations and avoid exercise (Crombez et al., 1998; Eccleston et al., 1999a; Torta et al., 2017a; Van Ryckeghem et al., 2018; Vlaeyen et al., 1995; Vlaeyen et al., 2000).

In summary, the cognitive-affective model focuses on explaining how cognitive and affective factors contribute to the selection of painful stimuli over other stimuli (Eccleston et al., 1999a). This theoretical framework identifies several cognitive and affective aspects of painful stimuli that moderate the interruptive strength of pain, including saliency and novelty. Cognitive factors such as saliency and novelty can disturb attention more than pain intensity, and facilitate attentional capture. In addition, affective factors including pain catastrophizing and hypervigilance can also increase the interruptive effects of pain on attention (Eccleston et al., 1999a).

3.3 The motivational account of attention to pain

The motivational account of attention to pain explains how goals affect the interplay between attention and pain, and is inspired both by Allport's model of attention (Section 2.1)

and the cognitive-affective model of the interruptive function of pain (Section 3.2) (Allport, 1989; Eccleston et al., 1999a; Van Damme et al., 2010b). According to this account, pain-related stimuli affect and disturb attention in two ways. First, pain-related information can involuntarily capture attention during pursuit of a non-pain-related goal, resulting in disruption of ongoing goals (i.e. bottom-up processes) (Crombez et al., 2013; Van Damme et al., 2010b; Van Ryckeghem et al., 2018). For example, one study examined the effect of pain on attention by using attentional tasks (including an endogenous pre-cueing task, n-back task, inhibition task, and divided attention task) under conditions of no stimulation, warm stimulation, and painful stimulation. The results indicated that pain impaired attention span (2-back task), attentional switching (cued number attentional shifting task), and divided attention (dual task in a visual modality), giving further support to the idea that painful stimuli can involuntarily reorient attention (Moore et al., 2012).

The second way pain-related stimuli can affect and disturb attention is via the activation of a pain-related goal (Eccleston et al., 2007; Van Damme et al., 2010b; Van Ryckeghem et al., 2012). In this case, prioritization of pain-related goals leads to increased attention on pain-related stimuli, resulting in inhibited processing of other information (Van Damme et al., 2010b). As an example, if we had back surgery last week, are working on an important task now, and once again feel pain, addressing it will likely become the central goal. As a result, attention to information unrelated to the back problem will be inhibited, and the performance of the original task will become less efficient. Similarly, for chronic pain patients who are affected and highly attentive to ongoing pain, pain management itself creates a goal that results in increased processing of pain-related information (Van Damme et al., 2010b; Van Ryckeghem

et al., 2018). In this case, selecting and focusing on pain over other information is driven by top-down mechanisms. In both cases, attention can facilitate pain processing when a goal is related to pain, such as trying to eliminate or control pain (i.e. top-down processes) (Torta et al., 2017a; Van Damme et al., 2010b; Van Ryckeghem et al., 2018). The motivational account of attention to pain model, builds up from the previously presented cognitive-affective model, which emphasizes the role of cognitive and affective factors in the interaction between painful stimuli and pain perception. However, according to this model the interaction between attention and pain needs to be studied within a framework of goal pursuit, in which pain and pain-related information can become the focus of attention.

The following paragraphs contain a brief description of the empirical evidence for attentional disruption by pain from two distinctive lines of research: evidence from studies in which pain was goal-irrelevant (bottom-up processing); and (2) evidence from studies in which pain was goal-relevant (top-down processing) (Van Damme et al., 2010b).

3.3.1 The effect of painful stimuli on attention when pain is irrelevant to the focal goal (bottom-up processing)

Many studies have examined attentional capture by pain using behavioral paradigms in which pain is irrelevant to the focal goal (Crombez et al., 1994; Eccleston, 1994). These behavioral paradigms, in which participants perform a cognitive task (e.g. an auditory detection or color discrimination task) while receiving a task-irrelevant painful stimulus, are designed to show that selection of painful information in an environment with multiple demands leads to

reduced attention to other information (i.e. the pain selection disturbs performance on the ongoing cognitive task) (Crombez et al., 1994; Crombez et al., 1996; Crombez et al., 1997; Crombez et al., 1998; Van Damme et al., 2010b). Comparing reaction time and accuracy in trials with pain to those without pain can reveal the attentional demand of pain in these behavioral tasks (Van Damme et al., 2010b). In one study, Crombez and colleagues recruited twenty-six healthy young volunteers to examine factors that can direct attention to pain. They designed an experiment in which a painful electrical stimuli and control pictures of a human face were presented prior to presentation of tone signals on which subjects performed a discrimination task. Findings showed that, compared to the control picture stimuli, painful electrical stimuli disturbed the performance of a tone discrimination task (Crombez et al., 1996).

Several neurophysiological studies have also confirmed that painful stimuli that are irrelevant to the main goal can capture attention (Van Damme et al., 2010b). For example, EEG studies have shown that nociceptive stimuli activated a cortical network (including prefrontal and posterior parietal areas) related to attention processes (Dowman, 2004; Seminowicz et al., 2007b). These studies found that novel nociceptive stimuli that are irrelevant to task goals increase the amplitude of the P2 component of the ERPs (Downar et al., 2000). Moreover, studies have revealed that nociceptive stimuli that could enhance P2 amplitude could also reduce reaction times to task-relevant visual targets (Downar et al., 2000; Legrain et al., 2003; Legrain, 2009). For example, one study examined the brain mechanisms underlying the interaction between nociceptive stimuli and attention processes by using laser- and visual-evoked potentials. Ten healthy young participants were recruited to perform a visual task where they instructed to count Xs that were presented onscreen while receiving novel and frequent

nociceptive laser stimuli. The findings of this study revealed that novel nociceptive laser stimuli increased all nociceptive-evoked brain potentials (N1, N2, P2) compared with frequent nociceptive laser stimuli. Reaction times were decreased during the reception of novel nociceptive laser stimuli compared with frequent stimuli. This suggests that the processing of irrelevant novel nociceptive stimuli decreases attention allocated to the processing of task-relevant information (Legrain, 2009).

Although these studies show that goal-irrelevant painful stimuli can attract attention, the results cannot prove a purely involuntary process caused entirely by bottom-up processing because participants will obviously be aware of painful stimuli presented during an experiment. Therefore, top-down processing might also increase attention to painful stimuli by classifying painful stimuli as goal-relevant information (Crombez et al., 2005; Dowman et al., 2008; Van Damme et al., 2010a; Van Ryckeghem et al., 2018). The following section reviews findings relevant to attentional processing when pain is goal-relevant.

3.3.2 The effect of painful stimuli on attention when pain is relevant to the focal goal (top-down processing)

Some studies have used a body-scanning paradigm to examine attentional processing when pain is goal-relevant (Peters et al., 2000). In one study the painful stimuli applied at only one of the four body sites. Participants had to detect painful stimuli by pressing buttons corresponding to that body location. The results showed that participants who reported higher

pain-related fear and higher levels of anxiety detected the locations of painful stimuli more quickly, suggesting that fearful and anxious participants have a strong tendency to scan their body for potential threats, which leading to increased attention to body signals (Peters et al., 2000; Van Damme et al., 2010a).

Some studies also investigated the impact of attention to goal-relevant pain using cueing paradigms (Van Damme et al., 2002). For example, in one study participants had to detect painful and auditory (tone) stimuli. Before each stimulus presentation, a word was displayed that either correctly or incorrectly cued the upcoming stimulus. The results showed that stimuli detection was faster following a correct cue compared to an incorrect one. Also, participant reaction times were decreased when the target was a tone stimulus that was incorrectly cued as a pain stimulus compared to when tone cues were matched with tone stimuli (Van Damme et al., 2004). Interestingly, participants who showed a high level of pain catastrophizing demonstrated faster pain detection compared to participants who showed a low level of pain catastrophizing. (Spence, 2004). These findings imply that pain detection was a higher priority goal compared to tone detection, particularly for people who had a high level of pain catastrophizing (Spence, 2004; Van Damme, 2004; Van Damme et al., 2010b).

Regarding the influence of attention over goal-relevant pain, some studies instructed participants to focus their attention on random painful stimuli while ignoring non-painful visual or auditory stimuli (Van Damme et al., 2010b). In these studies, brain activity during focused attention towards painful stimuli was compared to the activity that occurred when attention was directed towards non-painful stimuli (for a review, see (Lorenz et al, 2003). For example, one

study investigated the impact of selective spatial attention on laser-evoked potentials (LEPs) (Legrain, 2002). In that study, ten healthy young subjects performed a sustained attention target-detection task in which they had to attend to a particular hand during stimulation to both hands. The subjects received two different intensity and random painful stimuli on each hand. Their task was to focus on a particular hand and count the novel stimuli applied to target hand, while ignoring the other hand. They reported the number of novel stimuli at the end of each block. The results indicated that the attended, counted, and novel painful stimuli induced larger evoked responses. However, this effect was not observed when painful stimuli were delivered outside the focus of attention. These findings imply that particular features of the presented task and related attentional processes could affect distinctive stages of nociceptive processing in the brain (Bushnell et al., 1999; Legrain, 2002; Seminowicz et al., 2004; Van Damme et al., 2010b).

In summary, the motivational account of attention to pain explains how pain could affect and disturb attention through involuntarily capturing attention during the pursuit of a non-pain-related goal (bottom-up processes) or through the voluntary capture of attention when a pain-related goal is activated (top-down processes). Empirical evidence from studies in which participants instructed to detect, discriminate or evaluate their pain have revealed that attention is involuntarily directed toward painful stimuli even when these stimuli are irrelevant to a current goal. Furthermore, attention to pain increases when pain is relevant to a specific goal, leading to inhibited processing of other non-pain-related information (Van Damme et al., 2010b; Van Ryckeghem et al., 2018).

Thus far, it has been explained that the theoretical models of the interaction between

pain and attention – including limited attentional capacity theories (Section 3.1), the cognitive-affective model of the disturbing effect of pain (Section 3.2), and the motivational account of attention to pain (Section 3.3) – are all more focused on the interruptive effect of painful stimuli on ongoing cognitive goals. The next section (3.4) will address the neurocognitive model of attention to pain, which explains how WM can support attention in order to inhibit the disruptive effect of painful stimuli on ongoing cognitive goals (Legrain et al., 2009).

3.4 Neurocognitive model of attention to pain

Painful stimuli can disturb attention by disengaging the focus of attention from current goals towards painful stimuli. However, painful stimuli cannot always capture attention. The neurocognitive model of attention to pain proposes three factors that can inhibit the disruptive effects of painful stimuli on attention (Legrain et al., 2009).

The first factor, inspired by the concept of attentional set, is the mental set of the stimulus features (Gisèle, 2015; Legrain et al., 2013; Van Ryckeghem et al., 2013). Mental set refers to features related to the task-relevant stimulus, and must be identified in order to accomplish ongoing cognitive goals. The greater the distinction between the features of the target stimulus and the features of the pain stimulus and the features of a painful stimulus the less disruptive the painful stimuli will be (Legrain et al., 2013; Van Ryckeghem et al., 2013). For example, Legrain and colleagues designed an experiment where participants instructed to perform a color discrimination task (i.e. memorizing the color of two visual stimuli on a screen, in order to discriminate them from previous trails) along with randomly receiving painful stimuli (Legrain

et al., 2013; Legrain, 2011a). The colors of the visual stimuli defined the attentional set in that task. The results indicated that maintaining the attentional set of the task in WM (i.e. correct color) could shield task performance from painful distractions. This suggests that attentional set can modulate the effect of bottom-up processes induced by painful stimuli (Legrain et al., 2013; Legrain et al., 2011b; Legrain, 2011a). In summary, engaging attention to stimuli that are fundamentally unrelated to pain can inhibit the processing of painful stimuli (Gisèle, 2015; Legrain et al., 2013; Legrain et al., 2009; Torta et al., 2017b; Van Ryckeghem et al., 2013).

The second factor that can inhibit the disruptive effect of painful stimuli on attention is related to attentional load: if performance of the cognitive task requires more effort and more attentional allocation, the disruptive effect of painful stimuli will be decreased (Gisèle, 2015; Legrain et al., 2005a; Legrain et al., 2013; Romero et al., 2013; Torta et al., 2017a). This may be due to the fact that cognitive resources are limited and cannot fully support both the selection of goal-directed information (top-down attentional processes) and attention to painful stimuli (bottom-up attentional processes). Therefore, if cognitive tasks require effort – i.e. are demanding – less available resources will remain to process painful stimuli (Legrain et al., 2013; Legrain et al., 2009). For example, one EEG study investigated the effect of novel vs. frequent nociceptive stimuli on subject performance on high- vs. low-load visual tasks. The results indicated that novel nociceptive stimuli could elicit larger N2 and P2 amplitudes during the performance of the low-load visual task, and reaction times to visual targets were also longer with novel nociceptive stimulation, consistent with the cognitive-affective model (Legrain et al., 2013). However, during the performance of high-load visual tasks, which required greater attentional resources, the novelty effect on P2 magnitude was decreased. The results of

neuroimaging studies are also consistent with these findings. Several studies have revealed that the performance of a high-load cognitive task that is unrelated to pain significantly reduced brain activity associated with painful stimuli (Legrain et al., 2005a; Legrain et al., 2013; Legrain, 2012; Torta et al., 2017a). For example, one fMRI study investigated the brain activity related to painful stimuli during performance of a counting Stroop task with interference. This task was involved the presented words, which participants had to memorize the number of them (encoding phase), afterwards, one interference block consisting of numbers only was also presented between encoding and retrieval phase. Performance on the counting Stroop task was compared to performance on a low attentional demand task, in which the interference in the Stroop task was animal words, rather than number words (control condition). Participants received noxious thermal stimuli during both tasks. The results implied that engaging in a more cognitively demanding task could decrease pain intensity scores. This decrease was also correlated with decreased activity in specific regions of the pain matrix containing the mid-cingulate cortex, the primary and secondary somatosensory cortices, and the anterior insula. These findings support the hypothesis that performing a more cognitively demanding task can reduce pain perception (Bantick et al., 2002; Seminowicz et al., 2007a; Torta et al., 2017a).

The third factor that can inhibit the disruptive effect of painful stimuli on attention and support and control attentional engagement is executive functioning, specifically WM, which can guarantee the maintenance of goal priorities (Legrain et al., 2013; Legrain et al., 2009; Torta et al., 2017a; Van Ryckeghem et al., 2018). For example, one study examined the ability of WM to protect attentional capture by painful stimuli. ERPs were recorded while participants performed visual WM tasks with low versus high cognitive loads (0-back vs. 1-back conditions).

Somatosensory distractor stimuli were presented as non-painful electrical stimuli that were randomly replaced by nociceptive laser stimuli. In the low cognitive load condition (0-back), reaction times were increased in trials with the novel nociceptive distractors compared to trials with tactile distractors. However, these results were not observed in the high cognitive load condition (1-back), suggesting that engaging in a high WM load task inhibited interruption of the task by novel nociceptive distractors. Moreover, the magnitude of nociceptive ERPs was significantly decreased in the conditions involving high WM load, suggesting that WM can protect cognitive processing by inhibiting attention towards pain-related information (Legrain et al., 2013; Legrain et al., 2011b; Legrain, 2011a). The neurocognitive model of attention to pain proposes that top-down modulation of attention may be enhanced in people who show better WM performance. The reason is that better WM performance (inhibition, updating, and manipulation of information) is critical for the control of attentional capture and interference by painful stimuli (Legrain et al., 2013; Legrain et al., 2009).

To summarize, the neurocognitive model of attention to pain is focused on two types of attentional selection – bottom-up attentional capture and top-down modulation of attention – and their related brain structures. In this model, attention allocation to pain is affected by the trade-off between top-down and bottom-up processing. Bottom-up processing gives salient stimuli including painful stimuli more intense neuronal representation, leading to the involuntary capture of attention. (Legrain et al., 2009). However, decreasing the amount of attention paid to painful stimuli requires consideration of three related factors: attentional load, attentional set, and WM (Legrain et al., 2009; Torta et al., 2017a). Attentional load is the amount of attention allocated to a task; when attentional load increases, less available "space" remains

for painful stimuli within the focus of attention, as multiple sensory sources overload cognitive processing capacities. The attentional set is the maintenance of stimulus features in WM in order to identify goal-relevant information (Gisèle, 2015). WM is a temporary storage system which can actively maintain information and manipulate stored information. According to Baddeley and Hitch's model, WM includes a central executive component and two slave components (Baddeley, 2012). The central executive component of WM determines and prioritizes attentional set while the attentional load is determined and limited by WM capacity (i.e. the ability to actively store information despite ongoing processing, which is an indicator of limited cognitive resources) (see **Figure 4**) (Baddeley, 2003; Baddeley, 2012; Engle et al., 1999; Kane et al., 2001; Legrain et al., 2009; Torta et al., 2017a).

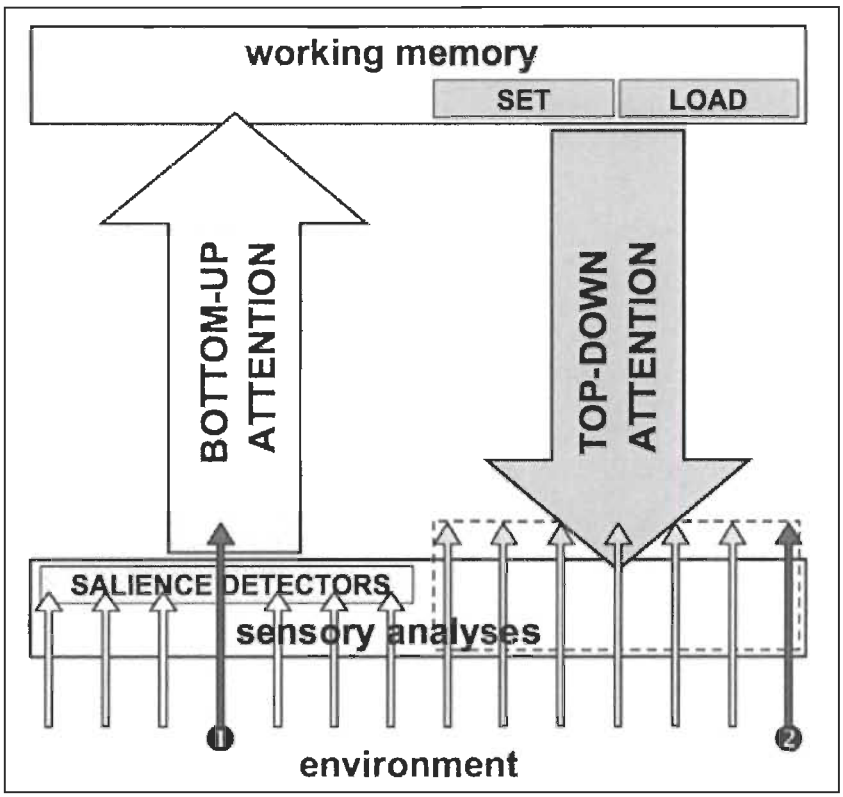

Figure 4. « Schematic representation of the neurocognitive model of attention to pain »

Bottom arrows show several incoming sensory signals from the environment, which the brain must prioritize as targets for entering into WM. Two types of selection are indicated here – bottom-up and top-down. Black arrow #1 shows the effect of bottom-up selection, which can detect salient stimuli. However, cognitive targets triggered in WM can guide top-down selection. Targets control which items are task-relevant ("attentional set") and the expanse of resources allocated to attain the task ("attentional load"). Grey arrows show increasing neural response to goal-relevant signals by top-down selection, while goal-irrelevant signals (white arrows) are inhibited by top-down selection. However, the model predicts attentional capture by salient stimuli through two ways. First, as is shown by black arrow #1, salient stimuli attract attention. Second, as indicated by black arrow #2, stimuli can grab attention when they share features with the attentional set. The figure is taken from (Legrain et al., 2009).

Regarding the neurocognitive model of attention to pain, the interaction between bottom-up and top-down attentional processes in pain is partially mediated by activity in the dorsolateral prefrontal cortex (DLPFC). The DLPFC participates in preserving goal-relevant information by biasing executive functioning, including WM, against goal-irrelevant stimuli. Moreover, the DLPFC is involved in pain processing. I will now review literature related to the role of the DLPFC role in both WM performance (Section 4.1) and pain (Section 4.2), and to explain the critical role that the DLPFC during pain regulation processes (Sections 4.2, 4.3, 4.4, 4.5).

4. DLPFC Function

The multidimensional nature of pain (i.e. sensory, emotional, motivational and cognitive components) cannot be associated with a single brain area or just one brain network. In order to find associations between pain regions and pain, it can be useful to combine neuroimaging methods (including electroencephalography, magnetoencephalography, and functional magnetic resonance) with noninvasive brain stimulation techniques (including transcranial direct current stimulation – tDCS – and repetitive transcranial magnetic stimulation – rTMS) that temporarily and noninvasively enhance or inhibit activity within specific brain regions. These new methods help to clarify the contribution of, and interaction between, these different aspects of pain and the different brain regions to identify the pain-related mechanisms (Seminowicz et al., 2017).

Neuroimaging studies have revealed that some brain areas are always engaged during the presentation of experimental nociceptive stimulation including the brainstem, thalamus,

primary and secondary somatosensory cortices, midcingulate cortex, and the insula (Duerden et al., 2013; Seminowicz et al., 2017; Wiech, 2016). Further, some of these areas show abnormal structure and function in chronic pain disorders, suggesting that they might be associated with nociceptive and/or pain processing (Bushnell et al., 2013; Davis et al., 2013). For example, the gray matter volume of the dorsolateral prefrontal cortex (DLPFC) is decreased in patients with chronic pain disorders such as chronic back pain, migraine, and trigeminal neuropathic pain, compared to that of healthy subjects (Apkarian et al., 2004; DaSilva et al., 2008; Seminowicz et al., 2017) for review see (Davis et al., 2013). Moreover, studies have reported that the DLPFC is involved in many cognitive processes including attention, WM, decision-making, and emotion regulation (Barbey et al., 2013; Buhle et al., 2014; Etkin et al., 2015; Philiastides et al., 2011; Seminowicz et al., 2017). A more detailed discussion of the critical role of the DLPFC in both cognition and pain is given in the following section.

4.1 The role of the DLPFC in working memory

The DLPFC is a functionally complex brain region in the prefrontal cortex that encompasses several Brodmann areas including 9, 8a, 8b, and the dorsal part of 46 (Sallet et al., 2013). The DLPFC is more extensive in humans compared with other primates, indicating its important role in complex cognitive processes (Nee et al., 2016). Our understanding of the functions of the DLPFC has mainly improved through the use two different types of neuroimaging methods. First, studies of resting state connectivity, performed in the absence of an overt task, have revealed the architecture of essential brain networks. A second type of study employs paradigms in which task performance, type, or perception are correlated with precise

locations, intensities, and time-courses of DLPFC activation (Biswal et al., 1995; Damoiseaux et al., 2006; Raichle et al., 2001; Smith et al., 2009). These neuroimaging studies could enhance our knowledge about the effect of the DLPFC in the processing of information for WM (Seminowicz et al., 2017).

One study investigated the essential role of the DLPFC in WM, by presenting WM tasks (e.g. the Wechsler Memory Scale and the n-back tasks) to three subject groups including patients with DLPFC lesions, patients with non-DLPFC lesions, and a healthy group with no brain lesions. The results showed that DLPFC damage was associated with deficits in the verbal and spatial manipulation of information, supporting the role of the DLPFC in WM processes (Barbey et al., 2013). Additionally, a review article focused on WM processes in monkeys supported the critical role of the DLPFC in WM performance. The findings in studies with monkeys showed that lesions in the dorsolateral areas of the prefrontal cortices impaired WM processes, compared to lesions in dorsomedial areas. This review article emphasized the role of the DLPFC in WM processes and proposed a functional dissociation between the dorsomedial and dorsolateral prefrontal cortices concerning WM function (Levy et al., 2000). Neuroimaging studies in humans have also revealed that the left DLPFC appears to support the manipulation of information in WM, whereas the right DLPFC is necessary for the manipulation of information in a range of reasoning contexts (Wager et al., 2003).

Studies in older persons have also revealed the effects of DLPFC in WM processes. For example, one study recruited sixteen healthy young and twenty older adults to perform blocks of encoding, retrieval, and control tasks. Participants had to memorize face/name stimuli pairs

presented on a screen during the encoding block. Three letters related to the first letter of the encoded stimuli name were presented during the retrieval block. In this block, participants had to identify a target letter within the three letters. During a control block, participants simply indicated when a particular visual target (a circle) was presented. The results indicated that decreased performance during information retrieval was associated with several brain areas including the left DLPFC, which showed significantly lower gray matter volume in older persons compared with younger adults. In particular, the findings revealed that high levels of activation in the DLPFC were negatively correlated with both grey matter volume and accuracy during the retrieval block in healthy older adults compared with younger adults (Kalpouzos et al., 2012). Generally, neuroimaging studies on aging, which aimed at examining the association between brain structure/function with cognitive performance, have found age-related under- and over-recruitment of brain regions (Kalpouzos et al., 2012; Maillet et al., 2013). Under-recruitment has been related to less efficient neural networks, while over-recruitment might be linked to compensatory mechanisms. According to the "Scaffolding theory," increased activity is an indicator of such compensatory mechanisms (Park et al., 2009). This increased brain activity is elaborated in response to the structural and molecular decline of the brain and in order to optimize cognitive performance (Park et al., 2009). Scaffolding theory proposed interactions between structural integrity and brain function (Park et al., 2009). The results of the Kalpouzos study -in line with this theory- showed that older adults undergo non-uniform gray matter volume loss. Therefore, local atrophy might partially affect functional brain activity in older adults. These findings indicated an interaction between age-related structural differences to age-related functional under and over-recruitment (Kalpouzos et al., 2012; Maillet et al., 2013; Park et al., 2009).

Another study examined the neural correlates of WM in twenty-eight healthy middle-aged adults, compared to thirty-four young adults. Facial stimuli depicting individuals of different ages were presented during the experiment, and the task was to memorize either the spatial location or the temporal order of six facial stimuli (low-load task) or twelve facial stimuli (high-load task). An fMRI scan was obtained from all participants during the encoding and retrieval phases of both the low- and high-load memory tasks. The findings showed that greater activation of the left DLPFC was positively associated with accurate performance during low-load tasks in healthy middle-aged adults. However, in young adults this association between greater activation and increased performance was only observed during the high-load task, suggesting that alterations in prefrontal cortex activation, including the DLPFC, can contribute to WM decline at midlife (Kwon et al., 2016). In summary, empirical evidence from animal studies, and human studies on both young and older persons supports a role of the DLPFC in WM processes, particularly in the central executive system that is responsible for the manipulation of information in WM. As mentioned in (section 3.4) WM processes include the encoding, storing, manipulation, and retrieval of information (Postle, 2006; Woodman et al., 2005). In line with this, Baddeley's WM model proposes three main WM components: the central executive system, which is responsible for manipulation of information and is also known as the supervisory attentional system; the phonological loop, which is responsible for storing and encoding verbal information; and the visuospatial sketchpad, which is responsible for storing and encoding visual information (Baddeley, 2012; Baddeley et al., 1974; Miyake et al., 1999). Regarding the processing of information in WM and Baddeley's WM model, studies have shown several brain areas to be activate during WM tasks. The superior frontal cortex is associated with information monitoring, updating, and manipulation during performance of WM

tasks. The ventral frontal cortex supports the rehearsal of information during information storage in WM. The anterior prefrontal, DLPFC, and ventral lateral prefrontal cortices mainly support the central executive system, which is responsible for the manipulation of information in WM (Wager et al., 2003; Wager et al., 2014).

4.2 The role of the DLPFC in pain

The DLPFC is not the only area active during pain, but it may be the central hub of networks supporting nociceptive processing and pain modulation (see **Figure 5**) (Glasser et al., 2016; Seminowicz et al., 2017). Studies have found activation of the DLPFC during the presentation of painful stimuli in healthy subjects, suggesting involvement of the DLPFC in pain perception (Lorenz et al., 2003; Seminowicz et al., 2017). For example, the DLPFC showed an 'all or none' response to pain stimuli despite varying intensities in stimuli or reported pain in healthy subjects, which suggests a role in pain detection (Bornhovd et al., 2002). Another study indicated that asking subjects to ignore pain resulted in increased bilateral activation of the DLPFC (particularly the left) during acute pain stimulation (Freund et al., 2009). Additionally, a study showed that left DLPFC activity was negatively correlated with the unpleasantness of painful thermal stimulation (Lorenz et al., 2003). Studies have also implicated the DLPFC in the placebo modulation of pain. For example, placebo analgesia studies have reported that inhibiting DLPFC activity blocked the placebo response, proposing a role of the DLPFC in integrating received nociceptive signals with pain expectation (Krummenacher et al., 2010; Petrovic et al., 2010; Wager et al., 2004). The DLPFC is also involved in the process of descending pain inhibition: the DLPFC can activate the ACC through synaptic connections.

Afterward, the ACC can activate the PAG, which can then activate different brainstem nuclei from which descending pain inhibition pathways originate. Activity along these pathways contributes to pain inhibition by modulating synaptic transmission in the dorsal horn of the spinal cord (Seminowicz et al., 2017; Tracey et al., 2007; Wiech, 2016). In summary, the findings have supported the role of the DLPFC in pain detection, emotional aspects of pain, and pain inhibition (Seminowicz et al., 2017).

4.3 The role of the DLPFC in cognitive components of pain

Evidence supports the involvement of the DLPFC in cognitive control over pain (Seminowicz et al., 2017). For example, the results of several studies in which participants had a sense of control over nociceptive stimuli have implicated the DLPFC in cognitive control over pain (Raij et al., 2009; Wiech et al., 2006). Other studies have revealed a negative correlation between pain-related activity in the bilateral DLPFC and pain catastrophizing (considered an indicator of dysfunctional cognitive control over pain), suggesting the involvement of the DLPFC in cognitive control over pain and pain-coping strategies (Seminowicz et al., 2006). In addition, cognitive control over pain involves a brain network including prefrontal areas (e.g. the DLPFC, ventrolateral prefrontal cortex, and orbitofrontal cortex, anterior insula, and anterior cingulate cortex) and brainstem areas (e.g. the periaqueductal gray and rostral ventral medulla)(Bingel et al., 2007b). One study showed that part of this brain network, including the DLPFC, anterior cingulate cortex, and cerebellum, might modulate the analgesic effects of spinal cord stimulation in chronic back pain patients, and implied that an interaction between peripheral and central mechanisms might reduce pain (Moens et al., 2012; Seminowicz et al.,

2017). In summary, the findings propose that the DLPFC might affect both cognitive control and pain modulation processes (Seminowicz et al., 2017).

The DLPFC is the central hub of at least three brain networks: the extrinsic mode network (EMN), the default mode network (DMN), and the cognitive control network. Distribution of cognitive resources during any cognitive task or sensory processing related to external stimuli is supported by the EMN network, whereas cognitive functioning related to monitoring internal processing and introspection of internal stimuli is supported by the DMN. The DLPFC is considered as a bridge to transfer information between the EMN and the DMN (Cole et al., 2007; Fox et al., 2005; Hugdahl et al., 2015; Raichle et al., 2001; Seminowicz et al., 2007c; Seminowicz et al., 2017). Regarding the activation of brain networks, pain can activate complex brain networks due to its multidimensional experience. This has been indicated in a study that aims to investigate the interaction between pain and cognition. For example, a study investigated the interaction between pain and cognition by asking participants to perform a cognitive task while they received painful stimuli. The result showed that activation in the ventrolateral part of the DLPFC was increased, and activation in the more dorsomedial part of the DLPFC decreased, while participants performed a cognitive task and received painful stimuli. These findings suggested that competing for cognitive resources led to an increase in the activity of the EMN and a decrease in the activity of the DMN during task performance. As a result, top-down modulation requiring active control over pain could also be affected by these limited cognitive resources (Norman et al., 1975; Seminowicz et al., 2007c). Therefore, designing interventions based on DLPFC activity and connectivity might be a promising approach for pain reduction (see **Figure 5**) (Seminowicz et al., 2017).

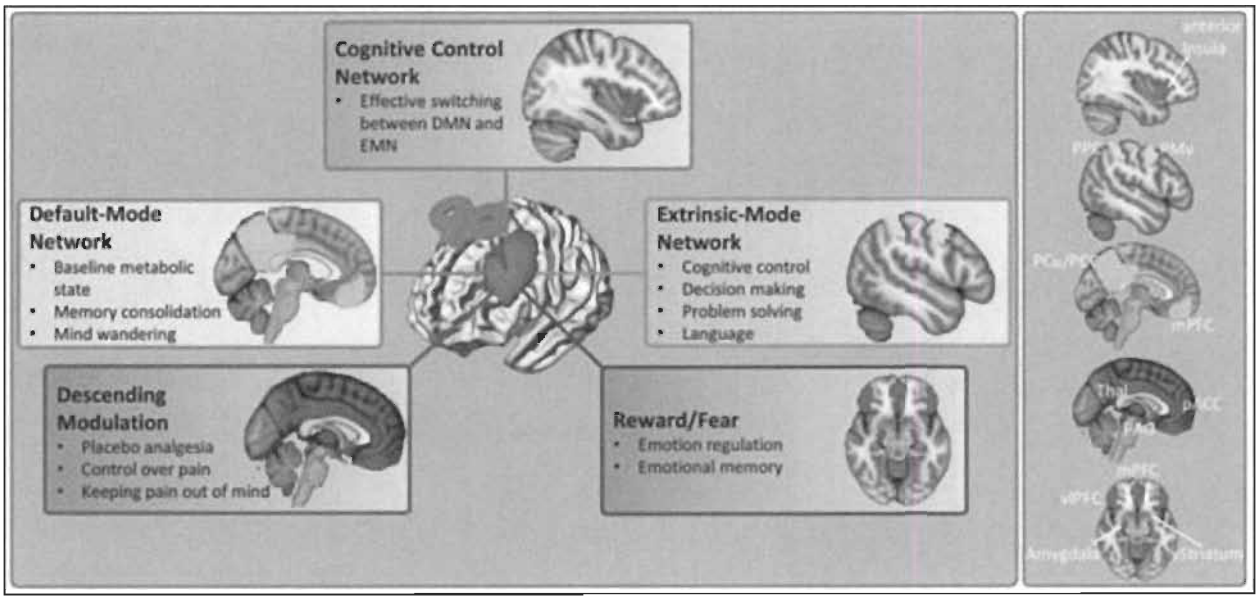

Figure 5. « The DLPFC function in pain »

"The DLPFC is a large and functionally heterogeneous region of the prefrontal cortex, which is indicated in dark green on a standardized brain in the center of the image. It is involved in several processes including pain regulation via several networks: controlling the regulation of cognitive networks (cognitive control network) through effective switching of the DMN and EMN; enhancing activity in a network involved in descending modulation of pain; and reducing emotional reactivity to pain through the reward/fear circuitry. The right panel provides the labels of the brain regions within each of these networks. PPC = posterior parietal cortex; PMv = ventral premotor cortex; PCu/PCC = precuneus/posterior cingulate cortex; mPFC = medial prefrontal cortex; Thal = thalamus; pACC = pregenual anterior cingulate cortex; PAG = periaqueductal gray; vlPFC = ventrolateral prefrontal cortex; vStriatum = ventral striatum. Figure is taken from" (Glasser et al., 2016; Seminowicz et al., 2017)

4.4 Abnormal DLPFC structure in chronic pain

Reduced gray matter volume in many cortical and subcortical brain areas is linked with chronic pain (Davis et al., 2013; Moayedi et al., 2012; Seminowicz et al., 2017). However, evidence suggests that appropriate pain interventions can partially reverse these structural changes (Seminowicz et al., 2011). For example, one study found that chronic back pain patients who received six-months of proper intervention (spinal surgery or facet joint block) showed a partial increase of left DLPFC brain gray matter (Seminowicz et al., 2011). This increase in left DLPFC gray matter was correlated with a decrease in clinical pain intensity and disability (Rodriguez-Raecke et al., 2009; Seminowicz et al., 2017). These findings along with those of similar studies suggest that the recovery of the DLPFC grey matter is a by-product of successful pain management interventions, thus it might be considered an indicator of effective treatment for pain conditions (Seminowicz et al., 2017).

Studies examining brain structure and function in chronic pain patients have improved our knowledge about the effect of the DLPFC in pain. For example, one study found reduced white matter connectivity between the midcingulate cortex and the DLPFC in patients with idiopathic temporomandibular disorder compared with the control group. They also reported abnormally increased activity of the left DLPFC compared with the control group during performance of a Stroop task (Moayedi et al., 2012; Seminowicz et al., 2017; Weissman-Fogel et al., 2011). Another study compared resting cerebral blood flow in chronic orofacial pain disorders (including patients with temporomandibular disorder and trigeminal neuropathic pain) with healthy controls (Youssef et al., 2014). The findings revealed that both patient groups

showed increased resting blood flow in the DLPFC compared with the control group. Other studies have reported lower gray matter volumes in the DLPFC of chronic pain patients (e.g. patients with irritable bowel syndrome, chronic low back pain, migraine, trigeminal neuralgia, chronic post-traumatic headache, and complex regional pain syndrome) suggesting the effect of DLPFC in pain conditions (Apkarian et al., 2004; Blankstein et al., 2010; Erpelding et al., 2016; Obermann et al., 2009; Schmidt-Wilcke et al., 2006; Seminowicz et al., 2010; Seminowicz et al., 2017; Seminowicz et al., 2011; Youssef et al., 2014).

Concerning functional connectivity studies in chronic pain patients, one study showed that patients with chronic migraine showed abnormal DLPFC connectivity compared to healthy participants (Hubbard et al., 2014). They showed decreased bilateral DLPFC connectivity to nodes of the DMN, and this decreased connectivity was negatively correlated with pain catastrophizing. Moreover, other studies have reported abnormal connectivity between the DLPFC and several brain regions in patients with chronic low back pain (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006; Seminowicz et al., 2011). Importantly, it appears that this type of abnormal connectivity can be partially reversed after a successful intervention (Seminowicz et al., 2011). The findings of one study showed that DLPFC activity was decreased in patients with chronic low back pain during performance a cognitive task compared to a control group of non-patients, but this decrease improved following effective treatment for the pain(Seminowicz et al., 2011). Chronic pain patients also show abnormal DLPFC connectivity between the DMN and the EMN (Ceko et al., 2015). Normalizing function of the left DLPFC, perhaps by cognitive coping strategies, might improve their cognitive ability, which in turn could lead to reduced pain (Seminowicz et al., 2017). Overall, these findings propose that a better understanding of DLPFC

function in chronic pain patients could contribute to more effective treatments (Seminowicz et al., 2017).

An additional point to consider is that DLPFC changes may not be related to pain, but may instead be secondarily associated with chronic pain. The findings of some studies have indicated that some common neural substrates, including the DLPFC, were shared in depression and chronic pain. Therefore, studies looking at the use of DLPFC stimulation as a treatment for depression might also find reduced chronic pain symptoms (Downar et al., 2013; Seminowicz et al., 2017). However, our knowledge in this field is currently limited, and is an essential need for the development of new chronic pain management tools (Seminowicz et al., 2017). The following section is a brief review of research that targeted the DLPFC using brain stimulation techniques including TMS and tDCS in order to lead to improvements in chronic pain conditions.

4.5 The DLPFC as a therapeutic target of brain stimulation techniques

The DLPFC is considered a potential therapeutic target due to evidence showing alterations in its structure and function in chronic pain patients, and its critical role in pain regulation (Brighina et al., 2004; Graff-Guerrero et al., 2005; Reid et al., 2001). In support of this, several studies have reported that noninvasive brain stimulation (rTMS and tDCS) of the DLPFC could alleviate both acute and chronic pain (Concerto et al., 2016; Conforto et al., 2014; Mylius et al., 2012b; Umezaki et al., 2016). For example, one study examined the effect of high-

frequency rTMS over the left DLPFC on chronic migraine (Brighina et al., 2004; Conforto et al., 2014). In general, rTMS can modulate cortical activity; low frequencies can inhibit activity, and high frequencies can increase cortical activity. In this study, eleven chronic migraine patients were recruited to receive twelve sessions of rTMS treatment delivered over the left DLPFC. They recorded attack frequency and headache frequency and severity in the months before, during, and following treatment. The findings showed that participants who received high-frequency rTMS had a significant decrease in headache frequency and severity during the month of treatment as well as the month following treatment, compared to the month prior to treatment. This implies that high-frequency rTMS over the left DLPFC could decrease chronic migraine frequency and intensity, which is consistent with the previously described effect of the DLPFC in pain inhibition (Brighina et al., 2004). In another study, pain induced by application of capsaicin was reduced by rTMS of the left DLPFC in healthy participants (Brighina et al., 2011). Additionally, other study has revealed that multiple sessions of active rTMS of the left DLPFC is an effective treatment for migraine and burning mouth syndrome (Brighina et al., 2011; Umezaki et al., 2016). The findings from studies in which tDCS was applied over the left DLPFC have also shown improved pain tolerance in healthy participants (the effect of tDCS on pain inhibition will be discussed in detail in Section 6) (Concerto et al., 2016; Lee et al., 2018; Volz et al., 2016). Interestingly, several studies have indicated successful treatment of major depression by rTMS of the left DLPFC (Lefaucheur et al., 2014; Lefaucheur et al., 2017). Treatment of depression alone may be beneficial for chronic pain patients as it can result in improved life quality and increases in health-promoting behaviors such as physical exercise, social interaction, and adherence to pain-reduction techniques. In summary, extensive evidence

supports the idea that targeting the DLPFC with brain stimulation techniques may be an effective intervention for the treatment of certain chronic pain conditions (Seminowicz et al., 2017).

It is still unknown whether activity of the DLPFC can be modulated by descending modulatory systems, cognitive or affective aspects of pain, or a combination of these mechanisms in healthy young or older adults. Empirical evidence supports the idea that older adults have decreased WM performance and decreased pain tolerance. Therefore, they are an appropriate target group for the study of cognitive modulation of pain. The following section will review findings related to both WM performance and pain in healthy older adults.

5. Motivation behind the choice of healthy older adults as subject group in the current work

As mentioned in previous sections, our attentional capacity is limited, as multiple sensory sources can overload our capacity and result in system competition (Kahneman, 1973; Kahneman et al., 1984; Legrain et al., 2009; Torta et al., 2017a; Van Damme et al., 2010b). Effective attentional control over pain entails more than simply disengaging attention from task-irrelevant pain stimuli; it is also necessary to maintain attention to task-relevant information (Legrain et al., 2013; Legrain et al., 2009). Many studies have demonstrated that WM allows us to maintain and prioritize task-relevant information in the face of task-irrelevant information such as painful stimuli (Legrain et al., 2011a; Legrain et al., 2013; Legrain et al., 2011b). However, age can influence the relationship between WM performance and pain (Oosterman et al., 2013). Given that WM performance is decreased in healthy older persons, it is plausible that

the ability to exert attentional control over pain is reduced as a result of impaired WM performance (Bopp et al., 2005; Borella et al., 2008; Darowski et al., 2008; De Beni et al., 2004). In addition, chronic pain conditions affect over 25% of people over 40 years of age (Frondini et al., 2007; Mansfield et al., 2016). Therefore, healthy older persons can be an appropriate target group in which to assess the interaction between WM performance and pain. Interestingly, whether brain stimulation techniques (e.g. tDCS) can effectively improve WM performance and in turn inhibit pain in this population is a missing piece in the literature.

The following is a brief overview of WM performance in healthy older persons (Section 5.1); pain perception in healthy older persons (Section 5.2); and the interactions between WM performance, pain, and aging (Section 5.3).

5.1 Working memory performance in healthy older persons

Aging is associated with several changes in the brain that affect global functioning, daily activity, and life quality. For example, studies have revealed that WM performance, particularly WM capacity, is reduced in healthy older persons (Bopp et al., 2005; Brink et al., 1999; Darowski et al., 2008; Zhou et al., 2015a). This reduction contributes to a reduction in the ability to inhibit distraction efficiently (Chai et al., 2018). Improving our knowledge regarding the interaction between WM capacity and distraction (such as by painful stimuli) may lead to developing effective assessment tools and appropriate interventions in order to inhibit pain in healthy older persons.

WM models have proposed several mechanisms that might be responsible for individual differences and age-related changes in WM performance. One of these mechanisms is called WM capacity: WM is the ability to store information while WM capacity is the maximum amount of information that can be stored – it varies from one individual to another (Barrett et al., 2004; Heitz et al., 2008; Kane et al., 2001; Kane et al., 2003; Rosen et al., 1998; Unsworth et al., 2006; Unsworth et al., 2009). The following sections are a brief overview of empirical evidence related to WM performance in healthy older persons.

5.1.1 Empirical evidence

Previous studies have investigated WM capacity in healthy older persons in two ways: first, through increasing WM loads, which can be done by increasing task demands; and second, through introducing distraction during tasks in order to disturb the WM process. Studies have shown that WM capacity is reduced in healthy older adults, which leads to a decreased ability to inhibit distraction efficiently (Borghini et al., 2018; Clapp et al., 2012; Gazzaley et al., 2005a; Kato et al., 2016; Keating et al., 2017; Lubitz et al., 2017; McNab et al., 2015; Zhou et al., 2015a). For example, one study recruited twenty-six healthy older adults (ages 60 – 82 years) and twenty-six healthy younger adults (ages 18–30) to examine age-related changes in WM performance by performing the span task and the delayed-response task. During the span task, participants were instructed to memorize two letters presented on the screen and repeat them out loud. The number of these letters was increased until participants could no longer correctly repeat them; this limit was used to define each participant's WM span. Afterwards, participants had to perform the delayed-response task, in which they had to memorize letters presented

sequentially during the encoding phase and, after a delay period, they had to recall those presented letters. The encoding phase contained either one letter (low load) or a number of letters corresponding to their WM span (high load). The delay phase contained either a distractor such as nine words, or no distractor and participants were simply presented with a fixation cross. During the delay phase, participants did not need to memorize or respond to the presented stimuli. The findings of this study implied that the accuracy of WM was decreased in older versus young adults during the high load WM task with distractors. Further, the maintenance of information in WM was overtaxed by high load tasks with distraction in older adults compared to young adults (Gazzaley et al., 2007).

Increased age is also related to a decreased ability to suppress the effect of distractors. Indeed, irrelevant information prevents or reduces the processing of relevant information, resulting in performance deficits in older adults (Darowski et al., 2008; Lustig et al., 2001). Many studies have confirmed age-related deficits in inhibitory control (Gazzaley et al., 2005b; Gazzaley et al., 2007; McNab et al., 2015; Yi et al., 2014). One, for example, tested the effect of presenting task-irrelevant distractors in older adults, using a visual n-back task (1-back and 2-back) in which Japanese words were presented with and without auditory distractors. In the 1-back condition, participants compared the Japanese words to the current stimulus immediately after it was presented; in the 2-back condition, participants provided a response to the stimulus presented two trials prior to the current trial. The results indicated that auditory distractions could significantly affect WM performance in the older group compared to the younger group, and this WM decline was primarily observed during the 2-back task (high load) (Kato et al., 2016).

Another study analyzed data from 29,631 users of a smartphone game and found that in older subjects, WM performance was affected more by distractors during the maintenance phase than during encoding. Indeed, the number of items that can be maintained in WM and the ability to inhibit distractors might both be reduced with increasing age and related to a decrease in WM capacity (McNab et al., 2015). Another study examined the influence of aging on three attentional control functions – shifting, inhibition, and updating – and their involvement in WM tasks. The participant group included 75 younger adults (mean age of 23.7) and 75 healthy older adults (mean age of 70.9). Complex WM tasks such as the Brown–Peterson procedure, in which participants were instructed to memorize three numbers while performing a simple addition task (adding one to random numbers during a short delay) were used along with tasks to measure attentional control functions such as the Stroop. The results showed that inhibition was reduced in older adults, suggesting that age affects inhibition (Sylvain-Roy et al., 2015). In addition, studies have shown that age-related declines in WM performance are affected by memory load and the presence of distractors, rather than by the type of information (e.g. visual or verbal) (Baddeley et al., 1974; Zhou et al., 2015a).

Evidence from electrophysiological and neuroimaging studies of age-related WM decline also supports the idea of age-related changes in WM processes (Gazzaley et al., 2005b; Keating et al., 2017; Lubitz et al., 2017; Yi et al., 2014). For example, one study tested the effect of age and individual differences on WM capacity by using electroencephalographic event-related potentials (ERPs). They recruited twenty healthy younger (ages 21–30 years) and twenty-one older adults (ages 62–79). To measure WM capacity, the O-span task was used, in which participants had to complete mental mathematics operations such as "(1x1) + 2 = ?" while

remembering 3 to 7 presented letters. In this study, the ability to prioritize goals was examined using a recognition exclusion task in which target words were encoded using two alternative techniques. The left parietal ERP was recorded as an electrophysiological index of recollection, and recollection was assessed through the change in the magnitude of the ERPs corresponding to recognized items. Greater recollection selectivity was observed in young adults with higher WM capacity than those with lower WM capacity, whereas lower recollection selectivity was observed in older adults overall, and it did not vary with WM capacity. These findings suggest that aging could be related to a decline in the ability to engage cognitive control and the ability to prioritize goals (Keating et al., 2017).

FMRI studies have revealed that reduced frontal activity is associated with increasing age, particularly in the face of distractors and increasing WM load (Amer et al., 2016; Darowski et al., 2008; Gazzaley et al., 2005b). Suppression of the default mode network (DMN) – which includes the medial prefrontal cortex, posterior cingulate cortex, and the posterior portion of the inferior parietal lobule – was decreased in older adults compared to younger adults. Indeed, the DMN network is involved in internally-focused cognitive processes, which are usually deactivated during tasks that require externally-driven attention such as WM tasks. Greater suppression of the DMN is related to improved performance on externally-driven attention tasks. However, older adults show a significant connection between the DMN and control brain areas during the performance of externally-driven attention tasks, indicating that the DMN interferes with cognitive performance in these subjects (Amer et al., 2016; Fox et al., 2005). In summary, theoretical models and empirical evidence confirm that WM function (including WM capacity and inhibition) might be reduced in healthy older adults particularly by performing

more demanding tasks. This reduction might in turn contribute to a decreased ability to inhibit distraction including painful stimuli (Amer et al., 2016; Chai et al., 2018; Gazzaley et al., 2005a; Gazzaley et al., 2007; Kato et al., 2016; Mitchell et al., 2000; Sylvain-Roy et al., 2015; Yi et al., 2014; Zhou et al., 2015a).

5.2 Pain in healthy older persons

Greater pain intensity, pain at more body locations, higher pain expectations, and the development of chronic pain disorders are reported more frequently in older adults compared to young adults (Hamerman, 1997; Leveille, 2004). Progressive musculoskeletal degeneration, as well as higher sensitivity to painful stimuli due to structural and functional changes in nociceptive systems, might lead to the higher prevalence of pain in older adults (Leveille, 2004; Riley et al., 2014).

Evidence from the literature suggests that pain in older adults (including sensory, affective, and cognitive aspects) differs from that of young adults (Petrini et al., 2015). For example, one study examined the effects of age on pain thresholds and pain tolerance and revealed that pain detection and tolerance thresholds were significantly decreased with age. In addition, the intensity and unpleasantness of pain stimuli were rated significantly higher in older compared to younger participants (Petrini et al., 2015). Another study examined responses to noxious stimuli in middle-aged and older adults, using a wide range of stimulus modalities. They measured participant responses to thermal, mechanical, and cold stimuli at the forearm and knee, in order to compare the impact of age on pain at different levels of spinal innervation.

The findings revealed that the older participants were less sensitive to warm and painful heat stimuli than middle-aged participants, especially at the knee, suggesting that pain sensitivity decreases with aging, perhaps particularly so in the lower extremities (Riley et al., 2014). The findings on pain sensitivity are variable due to different pain stimuli triggering different neural processes in aging (Chakour et al., 1996; El Tumi et al., 2017; Farrell, 2012; Gagliese, 2009; Lautenbacher et al., 2017).

5.3 Interaction between aging, working memory and pain

Aging affects the structure and function of brain areas such as the prefrontal cortex and hippocampus (Raz et al., 2010; Raz et al., 2005). These brain regions are involved in both pain processing (Zimmerman et al., 2009) and executive function including WM (Oosterman et al., 2008), suggesting a mechanism by which age-related cognitive changes in top-down pain modulation may also contribute to chronic pain conditions (Oosterman et al., 2013).

Presenting pain stimuli and cognitive tasks together requires dual information processing, which is extremely demanding. This dual information processing can be affected by age-related declines in cognitive resources, resulting in increased pain (Zhou et al., 2015a). For example, one study investigated the effect of age-related changes on pain inhibition in twenty-eight young (mean age = 24.8 years) and twenty-eight older adults (mean age = 67.5 years). In order to measure pain distraction, participants were instructed to perform a tonic heat pain test with and without distraction (i.e. they had to focus on a sound detection task). During intervals of the pain test, participants were also instructed to perform executive function tasks including

a WM task (1-back) and a response inhibition task (go/no-go). ERPs were recorded during performance of the cognitive tasks. Three ERP components including the P2, N2, and P3 were analyzed during the go/no-go inhibition task and the n-back WM task. This study focused on cognitive control processes at the two different early P2 and late N2 stages, inhibition processes (no-go P3), and attentional allocation in WM processes (n-back P3) in order to reveal the effects of aging on cognitive processing of pain. Previous studies have revealed that the P2 component (initiated by the orbitofrontal cortex) reflect early processes of top-down control over perceptual processing whereas the N2 component (initiated by the ACC) reflects target detection in the n-back task. The N2 in no-go trials (initiated by the orbitofrontal cortex and ACC) showed neural activity associated with conflict detection and inhibition processing. The n-back P3 component (initiated in parietal cortex) reflected neural activity related to attentional and WM processes. However, the no-go P3 component (initiated at frontocentral sites) reflected neural activity associated with inhibition processing. The results of this study shown that reported pain was significantly higher in older participants during the pain test with distraction, compared to without distraction. In parallel, younger participants showed an increase in brain activity of early processes (P2 component) in both go/no-go and 1-back tasks, which was correlated with lower pain reports during distraction. The older group, however, showed increased brain activity of later processes (N2 and P3 components), which are associated with WM processes, cognitive control, and attention. This increase in brain activity was also associated with higher pain reports during distraction. Indeed, the brain activity of early processes, which is associated with inhibition and WM tasks, was increased in the younger group. This result was correlated with lower pain reports in younger participants. However, the brain activity of later processes, which is induced by inhibition and WM tasks, was enhanced in older participants. This enhanced

activity of later processes was correlated with decreased pain in the older group. These findings imply that limited WM capacity in older adults, which might result from deterioration of frontal cerebral networks, may contribute to increased pain during distraction (Zhou et al., 2015b).

The interaction of aging, WM performance, and pain have also been examined in clinical populations including chronic pain patients. Cognitive deficits in various domains including executive function, attention, and WM have been observed in several pain conditions such as migraine (Mongini et al., 2005), fibromyalgia (Luerding et al., 2008), and diabetic neuropathy (Ryan et al., 1992). For example, one study compared patients with a diagnosis of chronic neuropathic or radicular pain to healthy controls using a battery of cognitive tests (Moriarty et al., 2017). The findings showed that cognitive performance was decreased in the patient group and that this decline was particularly evident in older patients. These results implied that pain can contribute to impaired cognition in chronic pain patients, and that this interaction between cognition and pain is affected by increasing age (Moriarty et al., 2017).

Studies on dementia and Alzheimer's patients have also explored the interaction between aging, WM performance, and pain. For example, one fMRI study examined brain responses to mechanical pressure stimulation in fourteen patients with Alzheimer's disease (mean age = 79 years) and fifteen age-matched healthy control volunteers (mean age = 79) (Cole et al., 2006). a higher amplitude and duration of pain-related activity in sensory, affective, and cognitive processing brain areas was shown in patients, along with sustained attention to the noxious stimuli. These findings imply that pain was not reduced in Alzheimer's disease patients (Cole et al., 2006). Another study has revealed that facial responses to painful pressure stimuli were

much more intense in dementia patients compared to controls (Kunz et al., 2007). These findings confirm the idea that dementia and Alzheimer's, which are associated with neurodegeneration in prefrontal areas, might contribute to a decline in executive function and decreased pain inhibition, making these patients more vulnerable to pain (Beach et al., 2016; Kunz et al., 2007).

Taken together, these findings are clear evidence of an interaction between aging, WM performance, and pain. Chronic pain may worsen with age-related cognitive decline, including a decline in WM. In addition, pain affects brain structure and function, which may contribute to declines in WM in older adults (Moriarty et al., 2014; Moriarty et al., 2011; Moriarty et al., 2017; Oosterman et al., 2013; Oosterman et al., 2016; Oosterman et al., 2008; van der Leeuw et al., 2016). Although there is no therapeutic intervention to improve WM performance, which in turn could lead to reduced pain, studies have revealed that anodal tDCS of the left DLPFC might improve WM (Brunoni et al., 2014; Fregni et al., 2005; Jo et al., 2009; Jones et al., 2015a; Mylius et al., 2012b; Plewnia et al., 2013; Wolkenstein et al., 2013; Wu et al., 2014). The following section describes evidence concerning the effects of tDCS on WM performance in both young and older adults as well as the effects of tDCS on pain perception.

6. Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation tool that has received much attention from researchers in recent decades for its use as a simple, painless, and economic rehabilitative treatment (André, 2016). TDCS delivers low direct current to the scalp via a small battery-driven stimulator connected to two electrodes of different polarities attached to the skin of the scalp. This device has two electrodes including an anodal (positively charged) electrode and a cathodal (negatively charged) electrode, for which the current and stimulation period can be easily controlled. One electrode is placed over a particular region of the brain, while the other – the reference electrode – is placed at another site on the opposite side of the body to complete the path (André, 2016). TDCS alters brain function by initiating resting membrane potential of a neuron or a neuronal pool into depolarization or hyperpolarization. Different types of stimulation by tDCS include anodal, cathodal, and sham. Anodal tDCS leads to depolarization of the resting membrane potential and results in increased neuronal excitability, whereas cathodal tDCS leads to hyperpolarization of the resting membrane potential and results in reduced neuron excitability due to reduced spontaneous cell firing. Sham stimulation produces a short current and then is shut off for the rest of the experiment. Sham stimulation allows researchers to compare the effects of anodal or cathodal tDCS with no stimulation and control for the placebo effect (André, 2016). To summarize, tDCS allows us to investigate human cortical functions by modulating cerebral excitability and affecting neuronal activation (André, 2016; Nitsche et al., 2008; Shin et al., 2015; Woods et al., 2016a).

Different forms of electrical brain stimulation have been used as a therapeutic technique for four centuries (André, 2016). For example, a study on anesthetized rats in the beginning of the twentieth century showed that intracerebral electrodes could deliver direct currents that induced depolarization of the resting membrane potential, which increased neuronal excitability over the sensorimotor cortex (André, 2016). Interestingly, this modulation of motor cortex excitability could persist for hours after the stimulation. The findings from EEG patterns and evoked potentials at the cortical level in humans have also confirmed this modification by tDCS. Recently, advanced neuroimaging methods including fMRI have provided an opportunity for researchers to study more clearly the effects of the tDCS technique in the human cerebral cortex (André, 2016; Nitsche et al., 2008; Shin et al., 2015). Additional experimental work may lead to better drug-based or alternative therapies for the treatment of clinical conditions including neurocognitive disorders and chronic pain. The following sections will overview the effects of tDCS on WM performance and pain in both young and older adults.

6.1 Effects of tDCS on working memory performance in young healthy adults

As it is mentioned previously, some critical cognitive abilities related to daily functioning depend on WM performance, which can be affected by the presence of distractions (Miyake et al., 1999). To assess WM performance, many studies use the n-back task, which requires monitoring a chain of visual or auditory information and comparing a new stimulus with a stimulus presented n trials before (Kane et al., 2007; Mackworth, 1959). Cognitive demands of the n-back task can be varied by asking participants to respond to the currently

presented stimuli (0-back) or one, two, or three stimuli presented before (1-back, 2-back or 3-back). The response times for stimulus detection and the rate of correct versus incorrect responses are used to evaluate performance on the n-back task (Jaeggi et al., 2010; Kane et al., 2007; Mackworth, 1959). In addition, WM depends on the activity of the frontoparietal network, mainly the DLPFC, which is associated with the encoding and updating of task-relevant information, and conflict resolution (André, 2016; D'Esposito et al., 2015; D'Esposito et al., 2000; Smith et al., 1997; Wager et al., 2003). Therefore, to assess the effect of tDCS on WM performance, several studies have hired the n-back task and have targeted the DLPFC region (André, 2016).

Regarding the effect of anodal tDCS over the left DLPFC on WM performance, Andrews and colleagues investigated the effect of applying tDCS over the left DLPFC (10 min at 1 mA) during the performance of a WM task on the performance of a subsequent WM task (Andrews et al., 2011b). Experimental conditions included either anodal tDCS during the performance of an n-back task, anodal tDCS during rest, or sham tDCS while performing an n-back task. Participants performed the WM task (2-back), followed by a 3-back task, and finally a digit span task. The latter task consists of the repetition of a series of numbers after presentation either in the same order (digits forward) or in the opposite order (digits backward). The tasks were performed immediately before and after each stimulation condition. The findings showed that applying tDCS during the n-back task could improve the performance of digit span forward, compared with applying tDCS during rest and sham tDCS during the n-back task conditions. It suggested that using tDCS during a WM task improved performance on a following WM task (Andrews et al., 2011b). In addition, Martin and colleagues examined the effect of applying

anodal tDCS over the left DLPFC (30 min at 2 mA) immediately before (offline tDCS) and during (online tDCS) the performance of an n-back WM task (Martin et al., 2014; Martin et al., 2013). They found that WM performance was significantly improved in participants who received anodal tDCS during the n-back WM task compared to those who received anodal tDCS immediately before the task (Martin et al., 2014)(Martin et al., 2014). Similarly, Gill and colleagues tested the effect of tDCS on tasks with different WM loads. The results revealed that the effects of anodal tDCS over the left DLPFC (20 min at 2 mA) on a WM task depended on whether participants performed the 3-back or 1-back task, suggesting that the effect of tDCS on WM are dependent on the cognitive demands of the task (Gill et al., 2015). Another study revealed that anodal tDCS over the left DLPFC (10 min at 1 mA) significantly increased the number of correct responses on a 3-back task, while there was no significant effect of cathodal tDCS over the same area or anodal tDCS over the primary motor cortex (André, 2016; Fregni et al., 2005).

Another set of findings in the study showed that anodal tDCS over the left DLPFC (15 min at 1.5 mA) combined with ten WM training sessions improved WM in the verbal domain, compared to sham tDCS (Richmond et al., 2014). Likewise, Martin and colleagues not only studied the effect of ten sessions of WM training combined with anodal tDCS but also re-evaluated WM performance four weeks after the experiment (Martin et al., 2013). Their results showed that anodal tDCS improved performance on the WM training task, and at the follow-up evaluation four weeks later, participants who received anodal tDCS combined with training showed more significant improvements on attention and WM tasks (untrained tests) compared to participants who received only anodal tDCS. These results imply that repeated sessions of

WM training combined with anodal tDCS over the DLPFC (30 min at 2 mA), compared to either training or anodal tDCS alone, may bring particular advantages in WM performance (Martin et al., 2013). In line with other studies, Zaehle and colleagues found not only that anodal tDCS over the left DLPFC (15 min at 1 mA) could improve WM performance, but also that application of cathode tDCS over the same region could disturb WM performance (Zaehle et al., 2011). Moreover, they used EEG to show possible neurophysiological alterations related to the effects of tDCS on WM. They found that applying anodal tDCS over the left DLPFC could increase activity in the theta band, which is related to memory encoding and retrieval (Jensen et al., 2002), as well as decrease activity in the alpha band, which is related to inhibition of irrelevant information and the maintenance of goal-relevant information (André, 2016; Zaehle et al., 2011).

Taken together, this evidence suggests that tDCS over the DLPFC (particularly left) can modify WM performance in healthy young adults. However, these findings are not entirely consistent. In order to reconcile inconsistent findings and optimize the beneficial effects of tDCS, two recent meta-analyses have suggested examining the effects of different stimulation parameters and study designs (Hill et al., 2016; Lefaucheur et al., 2017; Summers et al., 2016; Woods et al., 2016b).

6.2 Effects of tDCS on working memory performance in healthy older persons

Most of the research on the effect of tDCS on cognitive function in general, and WM performance in particular, have been conducted on young healthy participants, and only a few have investigated these effects in older populations (André, 2016). Only a few studies have tested the effectiveness of tDCS on WM performance in healthy older adults. For example, one study tested the effect of tDCS over the left DLPFC (30 min at 2 mA) on the performance of verbal and visuospatial WM tasks in healthy older adults. Twenty-four healthy older adults (ages 65-78 years) were recruited, and each received tDCS over the left DLPFC. The findings indicated that accuracy on the verbal WM task improved in the anodal tDCS group, compared to a sham group (Ho et al., 2011). Additionally, the findings of Berryhill study indicated that education level might modulate the effect of tDCS in older adults (Berryhill et al., 2012). In that study, tDCS was applied over the right or left DLPFC (10 min at 1.5 mA) before the subjects performed a WM task (visual or verbal 2-back). Twenty-five healthy older adults (ages 56–80) were recruited and divided into two groups according to education level (mean years of education: high = 16.9; low = 13.5). The findings of this study implied that participants with a higher level of education experienced a stronger effect of tDCS regardless of stimulation site or task type, indicating that the higher education group might employ a particular WM strategy that enhanced their DLPFC recruitment (André, 2016; Berryhill et al., 2012).

Many studies have only tested the effect of a single stimulation session. However, in order to produce long-lasting benefits from tDCS, several stimulation sessions might be more

effective. For example, Park and colleagues reported that ten WM training sessions combined with anodal tDCS (30 min at 2 mA) improved accuracy on a verbal WM task. They applied tDCS to the bilateral DLPFC (F3 and F4 sites) in forty healthy older persons (mean age: 69.7). Interestingly, this positive effect of tDCS lasted for one month. These results imply that tDCS combined with cognitive training can result in enhanced WM performance in healthy older persons, an effect that could be beneficial for older persons suffering from cognitive decline (Park et al., 2014). Likewise, Jones and colleagues studied the effect of ten sessions of anodal (10 min at 1.5 mA) and sham tDCS combined with WM training in seventy-two healthy older persons (ages 55–73). They divided participants into four groups, in which the electrode was placed over either the right prefrontal or parietal cortices, or alternated over both, during verbal and visual WM training tasks. Their findings showed that training could improve WM performance in all tDCS groups, but at a one-month follow-up evaluation, only the anodal tDCS group showed significant performance enhancement. These results imply that tDCS combined with WM training can provide long-term cognitive benefits (André, 2016; Jones et al., 2015a).

In summary, evidence from multiple studies suggests the effectiveness of using tDCS as a tool to preserve or improve cognitive function in healthy older adults (André, 2016). The aging process is associated with structural and functional alterations in the brain, such as increases in the distance between the brain and the skull and in the proportional volume of cerebrospinal fluid (CSF). As CSF has greater conductivity compared to cerebral matter and thus may change the current flow and reduce current intensity at the cortical surface, tDCS may differently affect aging brains (André, 2016; Beauchamp et al., 2011; Lockhart et al., 2014).

6.3 Effects of tDCS on pain

As it is mentioned before, chronic pain affects nearly 20% of the worldwide population and has an economic burden greater than cancer, heart disease, and HIV combined (Groenewald et al., 2014; Hogan et al., 2016; Moulin et al., 2002; Schopflocher et al., 2011). It is often resistant to treatment and the therapies that do exist are often associated with unwanted side-effects including opioid-based dependence and overdose (Gomes et al., 2013; Green et al., 2010; Lynch, 2011). Therefore, a critical need exists to develop alternative or supplemental treatment strategies, including non-pharmacological approaches. In line with this, empirical evidence supports a role for non-invasive brain stimulation techniques including tDCS, in the treatment of pain. This section will focus on an overview of evidence related to the effects of tDCS on pain in both young and aging healthy populations.

6.3.1 Effects of tDCS on pain in young healthy adults

Evidence suggests that tDCS can alleviate pain in healthy young adults. For example, one study examined the effects of anodal, cathodal, or sham tDCS over the left or right DLPFC on thermal pain in twelve healthy volunteers. The results revealed that anodal tDCS of the right DLPFC (15 min at 1 mA) increased tolerance to heat pain (Grundmann et al., 2011). Likewise, another study tested the effects of tDCS over the somatosensory cortex (15 min at 1 mA) on acute pain induced with a laser in ten healthy young subjects. A comparison of the pain ratings and amplitude changes of the N1, N2, and P2 components of laser-evoked potentials before and after anodal, cathodal, and sham tDCS revealed that cathodal tDCS significantly decreased pain

perception and reduced the amplitude of the N2 component, while no changes were observed in the anodal and sham stimulation conditions (Antal et al., 2008).

Boggio and colleagues assessed the ability of tDCS to modulate sensory and pain perception thresholds in twenty healthy young subjects. They applied tDCS under four different conditions: anodal tDCS (5 min at 2 mA) of the primary motor cortex (M1), DLPFC, occipital cortex, and sham tDCS. They showed that anodal tDCS over M1 and DLFPC could modulate pain thresholds (Boggio et al., 2008). Likewise, another study tested the effects of tDCS on subjective pain scores. Participants received 20 minutes of sham or anodal tDCS (2 mA) over the primary motor cortex before and after a single electrical stimulus over the right leg, which was followed by a series of five stimuli given at 0.5, 1, 5, and 20 Hz. The findings indicated that anodal tDCS over the primary motor cortex induced a significant analgesic effect at 20 Hz (Hughes et al., 2018). Mariano and colleagues also examined the effect of anodal tDCS over the left DLPFC (20 min at 2 mA) on the tolerability of acutely painful stimuli in forty healthy young volunteers. Their participants performed the cold pressor test and breath holding tasks during tDCS stimulation while rating pain intensity. The results showed that their pain ratings were significantly reduced by anodal vs. cathodal tDCS during the cold pressor test. To summarize, this evidence supports the ability of anodal tDCS, especially over M1 and DLFPC, to reduce pain in healthy young participants (Mariano et al., 2016).

6.3.2 Effects of tDCS on pain in healthy older persons

Most of the studies examining the effect of tDCS on pain reduction have used young healthy participants, while just a few have investigated this effect in older populations. For example, Ahn and colleagues tested the effect of five daily sessions of tDCS over the motor cortex (20 min at 2 mA) on experimental pain sensitivity in forty older adults (ages 50-70 years) with knee osteoarthritis. Participants responded to heat pain, pressure pain, punctate mechanical pain, and conditioned pain modulation. The results showed that thresholds and tolerances for all pain modalities significantly increased in the anodal tDCS group (Ahn et al., 2018). Likewise, another study investigated the effects of five sessions of anodal tDCS over the DLPFC (20 min at 2 mA) on pain perception and executive function in twenty-four older adults (mean age 71.25). Changes in pain perception were assessed using a visual analog scale, the Pain Self-Efficacy Scale, the Tampa Scale for Kinesiophobia (which assesses fear of pain), and the Global Perceived Satisfaction Scale, while a WM task and dual-tasking were used to detect changes in executive function. The results showed that anodal tDCS over the DLPFC might significantly reduce pain perception and improve quality of life, while executive function did not change (Lee et al., 2018). These findings are further evidence for the positive effect of anodal tDCS on pain perception in older adult populations (Lee et al., 2018).

Harvey and colleagues also assessed whether five days of tDCS application over the primary motor cortex could reduce pain and improve sleep in fourteen older participants (mean age 71±7 years) suffering from chronic pain and sleep complaints. They measured pain with visual analog scales, pain logbooks, and questionnaires, and sleep was measured with sleep

diaries and questionnaires. The results revealed that anodal tDCS over M1(20 min at 2 mA) significantly reduced pain but did not improve sleep (Harvey et al., 2017). Similarly, another study examined the effect of five sessions of anodal tDCS application over M1 with the goal of reducing chronic foot pain intensity and improving depression and pain-related anxiety symptoms in ten patients (mean age of 68.8) with treatment-resistant plantar fasciitis. They used a visual analog scale to assess perceived pain intensity, the Pain Anxiety Symptom Scale to assess anxiety, and the Hamilton Rating Scale to assess depression. They found that anodal tDCS significantly reduced pain intensity and pain-related anxiety and that this effect persisted up to four-weeks post-treatment. Additionally, patients reported taking fewer pain medication tablets after the treatments (Concerto et al., 2016).

Taken together, the evidence from numerous studies suggests that tDCS is a safe and well-tolerated procedure for the treatment of pain. However, many questions remain before tDCS can be widely and systematically used as a clinical tool. These include whether applying tDCS over the left DLPFC can improve WM performance in both healthy young and older adults, and in turn improve pain inhibition. What is the effect of differing WM loads? Does the pain modulation resulting from tDCS applied over the left DLPFC affect descending pain inhibition processes?

6.4 Conclusions

The effect of tDCS on WM is one of the fastest growing research topics in cognitive neuroscience today. Evidence from the studies reviewed in this section implies that tDCS is a

promising tool for the investigation of novel hypotheses regarding the improvement of WM performance of both young and older healthy adults (Andrews et al., 2011b; Brunoni et al., 2014; Hill et al., 2016; Jones et al., 2015b; Mylius et al., 2012b; Summers et al., 2016; Wolkenstein et al., 2013). Concerning pain perception, findings from several studies imply that tDCS can have a positive effect on pain not only in experimental pain but also in chronic pain conditions (e.g. migraine, fibromyalgia, and neuropathic pain) (Ahn et al., 2018; André, 2016; Concerto et al., 2016; Valle et al., 2009). Nevertheless, the effects of tDCS on pain inhibition are still a matter of debate in the literature.

To our knowledge, no study has investigated whether WM improvement by tDCS can enhance top-down inhibition of pain in either young or older populations. In the following sections, I will describe our motivations for performing the current work investigating the ability of tDCS to improve WM and in turn inhibit pain.

7. Motivations for current work

There are several motivations to perform my doctoral research projects. First, Legrain and colleagues introduced a neurocognitive model of attention to pain in which they emphasized the role of WM in pain modulation via top-down attentional control. They explained that pain is modulated by interactions between top-down and bottom-up processes. These interactions involve WM, which is partly supported by the activation of the DLPFC. Legrain and his team supported their model by several experiments employing laser-induced pain (Legrain et al.,

2013; Legrain et al., 2011b; Legrain, 2011a; Legrain et al., 2009; Legrain, 2012; Torta et al., 2017b).

Moreover, in regards to the work by Legrain and colleagues, there is a need to replicate their evidence using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission. In this case, we could also examine the effect of WM on pain inhibition, as well as the effect of WM improvement on descending inhibitory pathways (Ladouceur et al., 2017; Ladouceur et al., 2012b; Piche et al., 2011).

However, WM performance is impaired in patients with chronic pain as well as in healthy older populations (Baker et al., 2016; Berryman et al., 2013; Ferreira et al., 2016; Gazzaley et al., 2005b; Moriarty et al., 2011; Sambataro et al., 2010; Sammer et al., 2009). Understanding the interaction between WM enhancement and pain has important implications for clinical interventions intended to improve WM or treat pain in patient populations such as those with chronic pain or aging adults with deficits in WM performance. This raises the possibility that improving their WM performance may enhance their control over pain. However, no therapeutic intervention to date has been proposed that attempts to alleviate pain by improving WM performance. Interestingly, empirical evidence has confirmed that anodal tDCS over the DLPFC can improve WM performance (Andrews et al., 2011a; Jones et al., 2015a; Mariano et al., 2016; Mylius et al., 2012a; Park et al., 2014; Wolkenstein et al., 2013). Therefore, an outstanding question in the literature is whether this WM improvement by tDCS can enhance pain inhibition.

8. Methodological considerations

We carefully considered multiple methodological strategies for these projects. First, in order to test the specific inhibitory effect of WM engagement on pain perception, we used a modified n-back task with different WM loads (0-back and 2-back), as previously reported by the work of Legrain and colleagues (Legrain et al., 2013). We selected an n load of 2 after determining in a pilot study that the 3-back task was too difficult for participants.

Second, in order to recreate painful and tactile stimuli, transcutaneous electrical stimulation was delivered. The skin was stimulated by two adjacent pairs of electrodes placed over the retromalleolar path of the right sural nerve for the painful stimuli and on the dorsum of the foot for the tactile stimuli. For the painful stimuli, the NFR threshold was determined using the staircase method. The non painful electrical stimuli, which were used to make the painful stimuli novel and sufficiently salient and to limit the effect of alerting attention due to application of somatosensory stimulus, the detection threshold was defined as the first stimulus intensity that produced a tactile sensation under the electrodes. The painful and non_painful electrical stimuli were always delivered with the same pair of electrodes. Stimulus intensity was adjusted individually to 120% of the NFR threshold for painful stimulation and to 150% of the detection threshold for tactile (non-painful) stimulation. To make painful distractors more salient and novel, they were applied rarely and randomly among frequent non-painful stimuli. We compared conditions in which the n-back task was performed with or without painful distractors (Ladouceur et al., 2017; Ladouceur et al., 2012b; Legrain et al., 2013; Piche et al., 2011; Willer et al., 1989).

Finally, in order to determine the specific effect of anodal tDCS compared to sham tDCS and to control for non-specific between-session effects, we performed the experimental protocol twice during each session, once as a pre-tDCS baseline and once during tDCS. This allowed a within-session assessment of anodal tDCS and sham tDCS effects.

9. Project objectives and hypotheses

In the current projects, we examined whether pain inhibition by WM engagement can be enhanced by tDCS in young and older healthy volunteers.

In the first study, we hypothesized that anodal tDCS of the left DLPFC would improve WM performance, which in turn would improve top-down pain inhibition during performance of a cognitive task in young and older healthy volunteers (Hypothesis 1). We also investigated the interaction between task performance and pain perception and how WM could moderate these dynamics. We hypothesized that performing a WM task could decrease pain in young and older healthy volunteers (Hypothesis 2). We also examined whether pain inhibition by WM depends on descending inhibitory pathways, using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission (Hypothesis 3).

Next, we aimed to replicate and expand upon the results of our first study, using healthy older subjects in whom WM performance is usually reduced. We hypothesized that anodal tDCS of the DLPFC would improve WM performance, which in turn would improve top-down pain inhibition during performance of a cognitive task in older healthy adults (Hypothesis 1). We also examined whether pain inhibition by WM and its enhancement depend on descending inhibitory pathways, using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission (Hypothesis 2).

Chapter 2. Article of thesis

Enhancement of pain inhibition by working memory with anodal transcranial direct current stimulation of the left dorsolateral prefrontal cortex

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Running title: Enhancement of cognitive pain inhibition by tDCS

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Abstract

The aim of this study was to examine whether transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) enhances pain inhibition by improving working memory (WM). Forty healthy volunteers participated in two tDCS sessions. Pain was evoked by electrical stimulation at the ankle. Participants performed an *n*-back task (0-back and 2-back). The experimental protocol comprised five counterbalanced conditions (0-back, 2-back, pain, 0-back with pain and 2-back with pain) that were performed twice (pre-tDCS baseline and during tDCS). Compared with the pre-tDCS baseline values, anodal tDCS decreased response times for the 2-back condition ($p < 0.01$) but not for the 0-back condition ($p > 0.5$). Anodal tDCS also decreased pain ratings marginally in the 2-back with pain condition, but not the 0-back with pain condition ($p = 0.052$ and $p > 0.2$, respectively). No effect was produced by sham tDCS for any condition ($p > 0.2$). These results indicate that tDCS of the left DLPFC may enhance pain inhibition by improving WM.

Keywords Neuromodulation · Nociceptive · Cognition · Descending modulation · Anxiety

1. Introduction

Limited-capacity models of cognition posit that a sensory signal must be selected for optimal perception because multiple sensory sources from the environment overload cognitive processing capacities (Barcelo et al., 2006; Berti et al., 2004; Legrain et al., 2009; Legrain, 2012; McCaul et al., 1985). In line with these models, executive functions allow the selection of stimuli depending on their priority, in order to uphold the execution of a task or to promote most adapted goal-directed behaviors (Awh et al., 2006; Corbetta et al., 2002; Legrain et al., 2011a; Legrain et al., 2013; Legrain, 2009; Torta et al., 2017a; Verhoeven et al., 2011). For instance, a nociceptive stimulus may be selected to prioritize protective behaviors at the expense of task performance (Bingel et al., 2007a; Downar et al., 2003; Egeth et al., 1997; Escera et al., 2007; Knudsen, 2007; Legrain et al., 2009; Legrain, 2009; Yantis et al., 1990). Conversely, pain perception can be inhibited by cognitive processes if task execution is prioritized, in accordance with contextual demands (Bingel et al., 2007a; Hopfinger et al., 2006; Legrain et al., 2011a; Legrain et al., 2013; Legrain, 2002; Seminowicz et al., 2007b; Seminowicz et al., 2007c). The balance between these bottom-up and top-down processes is critical for optimal behavioral performance, behavioral adaptation and survival (Berti et al., 2004; Corbetta et al., 2002; Legrain et al., 2009; Legrain, 2012; Miyake et al., 2000; Torta et al., 2017a).

Bottom-up processes give salient stimuli a stronger neuronal representation. For instance, nociceptive stimuli are intrinsically salient and capture attention (Egeth et al., 1997; Knudsen, 2007; Yantis et al., 1990). However, attentional capture may be influenced by top-down processes (Folk et al., 1992; Hopfinger et al., 2006; Van Damme et al., 2010b). Top-down

selection is determined by cognitive goals represented in working memory (WM) (Legrain et al., 2011b; Legrain et al., 2009; Miller et al., 2001; Miyake et al., 2000; Soto et al., 2008; Tracey et al., 2007). Cognitive goals determine which stimuli are task relevant (attentional set) (Crombez et al., 1998; Legrain et al., 2009) and the amount of attentional resources allocated to achieve the task (attentional load) (Lavie et al., 2006; Lavie et al., 2004; Legrain et al., 2005b; SanMiguel et al., 2008). This is supported, in part, by the activation of the dorsolateral prefrontal cortex (DLPFC), which is involved in WM and in the allocation of attentional resources (Awh et al., 2006; Barcelo et al., 2006; D'Esposito et al., 2000; Hester et al., 2005; Lavie et al., 2006; Lavie et al., 2004; Legrain et al., 2013; Legrain et al., 2009; Levy et al., 2000; Miller et al., 2001; Soto et al., 2008; Szmalec et al., 2011). According to the model of Baddeley and Hitch, WM comprises a central executive component and slave components that include rehearsal and storing functions (Baddeley, 2003). The central executive component of WM determines the attentional set while the attentional load is determined and limited by WM capacity. During pain perception, effective attentional control not only depends on the disengagement of attention from pain but also on the allocation of cognitive resources to maintain attention on the processing of task-relevant information unrelated to pain (Buhle et al., 2010; Crombez et al., 1998; Legrain et al., 2011a; Legrain et al., 2013; Legrain et al., 2011b; Legrain et al., 2009). Consistent with this, WM allows the selection of task-relevant information and allows attention to be directed towards task execution (Awh et al., 2001; Berti et al., 2003; Hester et al., 2005; Jan et al., 2001; Legrain et al., 2011a; Legrain et al., 2013; Legrain et al., 2009; SanMiguel et al., 2008; Soto et al., 2005; Wager et al., 2014). This results in top-down regulation of attention in line with current goals, while nociceptive activity and subsequent pain perception are inhibited.

Top-down inhibition of nociceptive activity and pain may be altered in patients with chronic pain (Baker et al., 2016; Berryman et al., 2013; Ferreira et al., 2016; Moriarty et al., 2011) and in normal aging (Gazzaley et al., 2005b; Mitchell et al., 2000; Sambataro et al., 2010; Sammer et al., 2009) due to decreased WM. Yet, no therapeutic intervention has been proposed to alleviate this reduction of WM performance. Transcranial Direct Current Stimulation (tDCS) is a promising method in this regard since anodal tDCS of the left DLPFC was shown to improve WM performance (Andrews et al., 2011b; Berryhill et al., 2012; Boggio et al., 2006b; Brunoni et al., 2014; Hill et al., 2016; Jo et al., 2009; Mariano et al., 2016; Mylius et al., 2012b; Park et al., 2014; Wolkenstein et al., 2013). However, whether this WM improvement may enhance top-down regulation of nociceptive activity and pain has not yet been studied. Thus, the aim of the present study was to investigate whether pain inhibition by WM engagement can be enhanced by tDCS in healthy volunteers. We hypothesized that anodal tDCS of the left DLPFC would improve WM performance, which in turn, would improve top-down pain inhibition during a cognitive task. We also examined whether pain inhibition by WM and its enhancement depend on descending inhibitory pathways, using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission.

2. Methods

2.1 Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of Université du Québec à Trois-Rivières. All participants gave written informed consent, acknowledging their

right to withdraw from the experiment without prejudice and received a compensation of $50 for their travel expenses, time and commitment.

2.2 Participants

Forty healthy volunteers (23 women and 17 men; range 19-38 years; mean ± SD: 25.77 ± 4.61 years) were recruited by advertisement on the campus of Université du Québec à Trois-Rivières. Participants were included if they were between 18 and 40 years old with normal or corrected-to-normal vision. They were excluded if they had taken any medication within two weeks before the experiment and if they had a history of chronic pain, suffered from acute or chronic neurological illness or if they had a psychiatric disorder. Two participants could not complete the experimental procedures. In one participant, the NFR could not be evoked at a stimulus intensity that was tolerable for the participant in the context of this study. The other participant could not perform the n-back task. Therefore, data from these two participants were not collected, leaving a sample of 40 participants with the characteristics reported above.

2.3 Experimental design

This experiment is based on a double-blind sham-controlled design to determine the effect of a single anodal tDCS session applied over the left DLPFC on WM and pain inhibition by WM. A modified n-back task was used and consisted in color discrimination of blue and yellow squares by pressing the corresponding button (Legrain et al., 2011b). In order to obtain two different levels of WM load, the n-back task was either 0-back, discriminating the color of

the presented stimulus, or 2-back, discriminating the color of the stimulus presented two trials earlier. WM load is greater in the 2-back task because stimuli have to be remembered for two trials while subsequent stimuli are presented. This leads to stimulus property storage, rehearsal and updating, in addition to stimulus selection and discrimination, which are also required in the 0-back task. The painful stimuli were delivered alone or concurrently to the n-back task to test the interaction between WM and pain.

2.4 Transcutaneous electrical stimulation on the foot

Transcutaneous electrical stimulation (trains of 10 x 1-ms pulses at 333 Hz) was delivered with two isolated DS7A constant current stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA, USA) that was controlled by a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). The degreased skin was stimulated by two adjacent pairs of custom-made surface electrodes (1 cm^2; 2 cm inter-electrode distance) placed over the retromalleolar path of the right sural nerve for the painful stimulus and on the dorsum of the foot for the tactile stimulus. For the painful stimulus, the NFR threshold was determined using the staircase method (Ladouceur et al., 2017; Ladouceur et al., 2012a; Piché et al., 2011; Willer, 1977), including four series of stimuli of increasing and decreasing intensity. Each series began with a stimulus intensity of 1 mA and was incremented by steps of 1 mA, reaching a suprathreshold level between 15 and 25 mA (clearly above the threshold but adjusted individually to avoid severe pain). Stimulus intensity was then decreased by steps of 1 mA. After 4 of those series were completed, NFR amplitude was plotted against the stimulus intensity

(recruitment curve) and threshold was defined as the intensity producing a clear response exceeding background EMG in at least 50% of trials. Background EMG was defined as the maximum artefact free EMG activity observed in the same post-stimulus interval of 90-180 ms across all sub-threshold stimuli. For the tactile stimulus, the detection threshold was determined as the first stimulus intensity that produced a tactile sensation under the electrodes. The painful and tactile stimuli were always delivered with the same pair of electrodes. In both sessions, stimulus intensity was adjusted individually to 120 % of the NFR threshold for painful stimulation and to 150 % of the detection threshold for tactile (non-painful) stimulation.

2.5 NFR measure and analysis

Electromyography (EMG) of the short head of the right biceps femoris was recorded with a pair of surface electrodes (EL-508, Biopac Systems, Inc., Goleta, CA, USA). It was amplified 2000 times, band-pass filtered (10-500 Hz), sampled at 1000 Hz (Biopac Systems, Inc., Goleta, CA, USA) and stored on a personal computer for off-line analyses. The raw EMG recordings were full-wave rectified and the resulting signal was used to quantify the amplitude of NFR to each shock by extracting the integral value between 90-180 ms after stimulus onset. This amplitude was standardized using a within-subject z-transformation. For group analyses, the mean response to 10 painful stimuli was calculated for each condition.

2.6 Pain and pain-related anxiety ratings

Participants verbally rated pain intensity and pain-related anxiety using numerical rating

scales (NRS) with two anchors on the left and right extremities (0, no pain/anxiety and 100, extreme pain/anxiety). These scales were displayed horizontally on a computer screen after each condition.

2.7 Transcranial direct current stimulation

A direct current of 2 mA was generated by a battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) and delivered continuously using a pair of rubber electrodes (35 cm^2 surface) covered by conductive sponges moistened with saline. To enhance the activity of the left DLPFC, the anodal electrode was placed on the scalp over the F3 site, according to the International 10-20 system of electrode placement. The cathode was placed over the right deltoid muscle to make sure that tDCS effects were due only to anodal stimulation (Wolkenstein et al., 2013). During the first 30 seconds of stimulation, the current was ramped up to 2 mA and then delivered for 22 minutes. The first 3 minutes allowed participants to get used to tDCS before begining the task. At the end of stimulation, the current was ramped down to 0 mA over 30 seconds. For the sham stimulation, electrodes were placed in the same positions but the current was only applied for 46 seconds. Predefined codes assigned to either sham or anodal stimulation were used to start the stimulator. These codes allowed for a double-blind study design. The order of tDCS and sham sessions was counterbalanced across participants with a one-week inter-session interval. Participants were unaware that tDCS stimulation was different between sessions and they were not informed that we were testing the effects of two different types of tDCS stimulation. They were informed that they may feel itching or burning but that this was variable between individuals. Participants reported slight itching with the tDCS stimulation in

both sessions, especially at the begining of the protocol. Although participants may have felt more itching with anodal tDCS, they did not know if this was to produce greater effects on pain or task performance.

2.8 n-Back task

A modified n-back task was used (Legrain et al., 2013; Legrain et al., 2011b) in which the participant had to discriminate between blue and yellow squares with two levels of WM load (0-back and 2-back). WM performance was examined with two measures, including response time (RT) and response accuracy (RA: percentage of correct responses). The mean RT was calculated for each condition by including RTs from each trial with a correct response. Trials with incorrect responses, trials defined as anticipated responses (RT < 150 ms), or with missed responses were excluded from the mean RT calculation.

For conditions with electrical stimulation during the n-back task (0-back or 2-back), a series of task-relevant stimuli (blue or yellow squares presented for 500 ms) were shortly preceded by a task-irrelevant tactile stimulus (see Figure 1). Occasionally, the tactile stimulus was replaced by a painful stimulus as described in a previous study (Legrain et al., 2013), in order to keep the novelty of painful stimuli. The inter-stimulus interval (ISI) between the onset of the electrical stimulus and the onset of task-relevant stimulus was either 220 ms for tactile trials and 300 ms for painful trials, in order to account for the conduction velocity of tactile and nociceptive fibers (Legrain et al., 2013). The inter-trial interval (ITI) between the onsets of two consecutive task-relevant stimuli was 3000 ms.

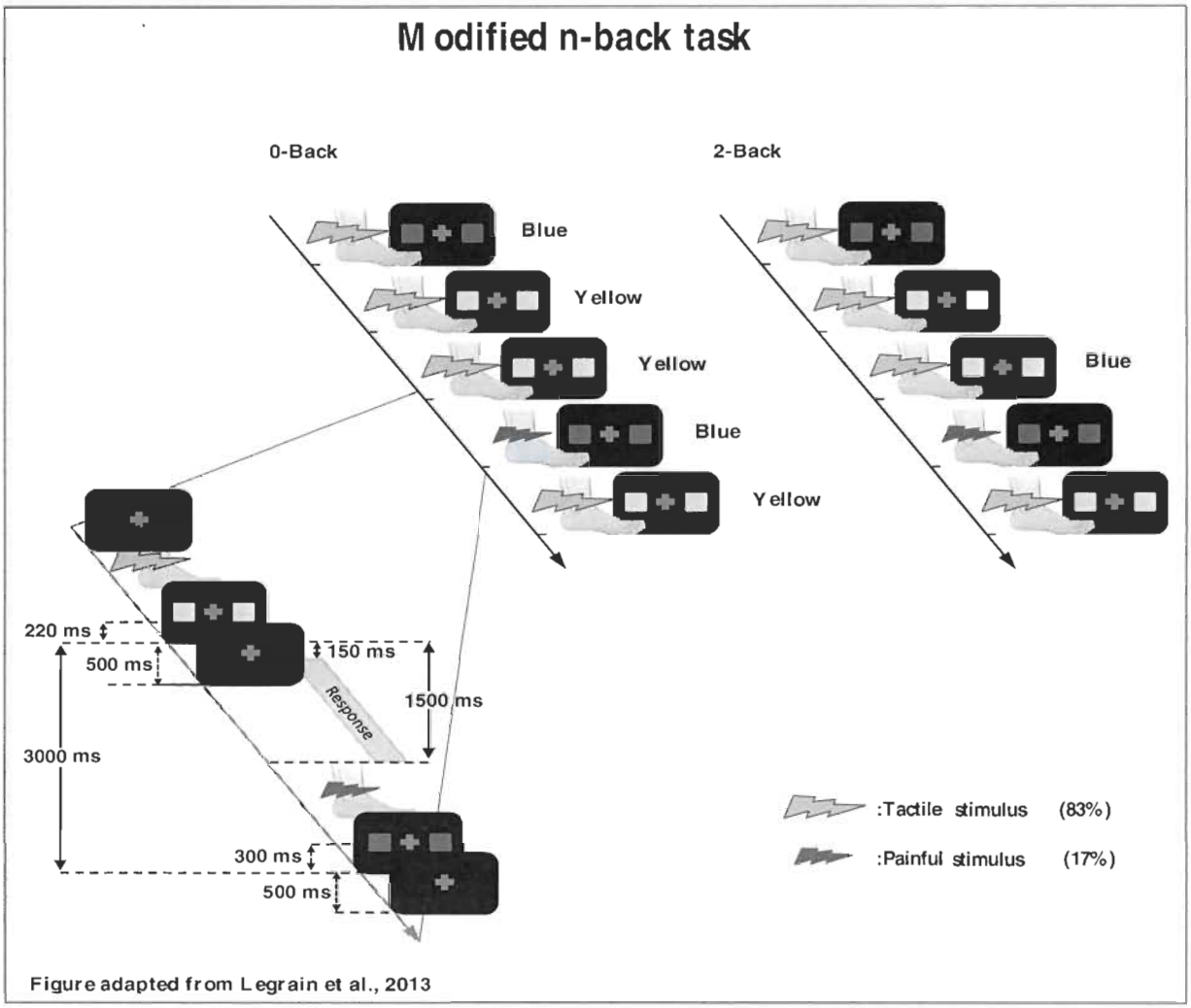

Figure 6. Modified n-back task.

Participants performed a modified n-back task in which they had to discriminate the color of each visual stimulus constituted of two squares which were either both blue or both yellow. In the 0-back condition, participants discriminated the color of the current stimulus directly after its presentation; in the 2-back condition, they responded to the stimulus presented two trials before. The visual stimulus was preceded by a tactile stimulus in 83% of trials or by a painful stimulus in the remaining trials (17%). Bottom left panel Sequential timings of stimuli in each trial. A fixation cross was present at the center of the screen during the entire trial. Electrical

stimuli were followed by a visual stimulus of 500 ms duration. The interval between the somatosensory and visual stimuli (ISI) was 220 ms for the tactile trials and 300 ms for the painful trials. Performance in the modified n-back task was measured in the time window running from 150 to 1500 ms after onset of the visual stimulus. The next trial started at a latency set so that the inter-trial interval (ITI) measured between the onsets of two consecutive visual stimuli was 3000 ms

2.9 Experimental procedure

Participants completed two 180-minute sessions on separate days with a 1-week interval. All participants received anodal brain stimulation and sham stimulation in a counter-balanced session order. The same protocol was carried out for both sessions. After individual adjustment of stimulus intensities, the tDCS electrodes were placed as described above and participants were allowed to get familiar with the n-back task. Familiarization included twenty trials for each condition (0-back and 2-back) during which participants received visual feedback (correct or incorrect response). After this practice, the experimental protocol began with the pre-tDCS baseline conditions (0-back, 2-back, pain, 0-back with pain, 2-back with pain) followed by the same five conditions during tDCS (see **Figure 7**). Each condition included 60 trials. For the 0-back and 2-back conditions, the 60 trials were presented without any electrical stimulation. For the pain condition, the 60 trials included 50 tactile stimuli and 10 painful stimuli without the n-back task. For the 0-back and 2-back with pain conditions, 50 trials of the n-back task were preceded by tactile stimulus while 10 trials were preceded by the painful stimulus. The order of the five conditions was counterbalanced between subjects but the same order was kept for the

pre-tDCS baseline and tDCS conditions. In addition, the order was kept the same within participant for both sessions (anodal and sham).

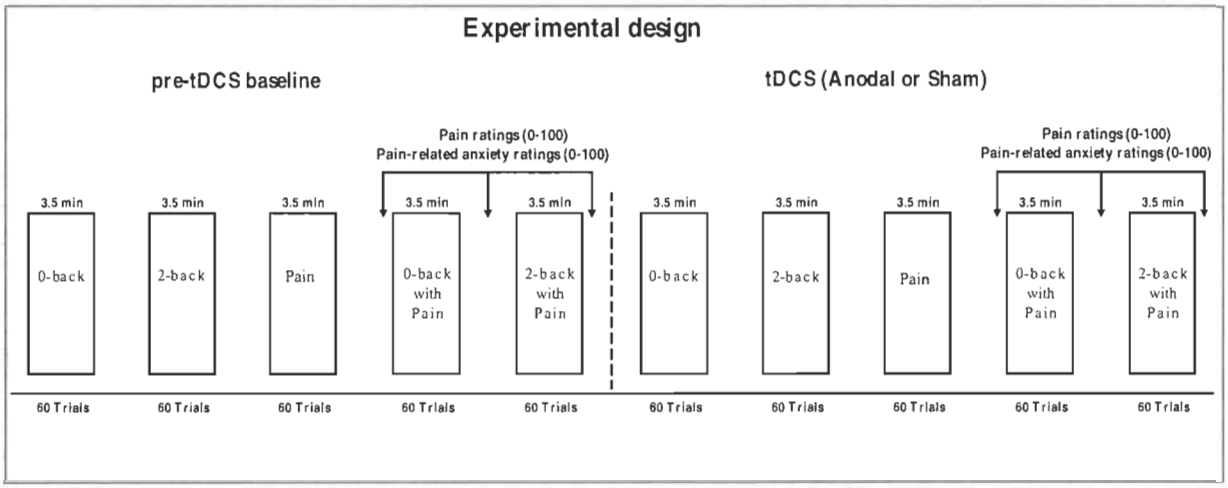

Figure 7. Experimental design.

The experimental protocol comprised five counterbalanced conditions, including the 0-back, 2-back, pain, 0-back with pain and 2-back with pain conditions. This experimental protocol was performed twice during each session, once to establish a pre-transcranial direct current stimulation (tDCS) baseline and once during tDCS. The same order was used for the sham and anodal tDCS sessions for a given participant. Each condition contained 60 trials within 3.5 min. Participants had to verbally rate their average pain and their pain-related anxiety using a numerical rating scale (NRS; range 0–100) after each condition comprising painful stimuli.

2.10 Statistical analysis

Data Analysis was conducted by Statistica v13 (Dell Inc., Tulsa, OK, USA). All results are expressed as mean ± SEM and statistical threshold was set to $p \leq 0.05$ (two-tailed). A priori hypotheses were tested with planned contrasts and the type I error rate was controlled for using the Bonferroni correction for multiple comparisons, based on the number of comparisons for each independent analysis. All reported p-values are therefore corrected for multiple comparisons for all variables, including RT, RA, pain, pain-related anxiety and NFR amplitude. Effect sizes are reported based on partial eta- squared values (ηp2).

3. Results

3.1 Manipulation checks

Pre-tDCS baseline values are presented in (**Table** 1. Manipulation checks. To confirm that experimental effects crucial to test our hypotheses were observed prior to the tDCS intervention, we performed Bonferroni-corrected planned contrasts to show that WM was unaffected by painful stimuli and that pain was inhibited by the engagement of WM. Accordingly, in the anodal tDCS session, pain did not significantly affect RT or RA for either the 0-back or the 2-back tasks (RT: $p > 0.6$, $\eta^2 < 0.01$; RA: $p > 0.2$, $\eta^2 < 0.01$). Likewise, in the sham pp tDCS session, pain did not significantly alter RT or RA for either the 0-back or 2-back tasks ($p > 0.7$, $\eta_p^2 \leq 0.04$; $p > 0.2$, $\eta_p^2 = 0.11$ and < 0.01, respectively).

As expected based on prior studies [68], pain perception was decreased by WM for both the 0-back and 2-back tasks in the anodal tDCS session ($p = 0.04$ and $p = 0.003$, $\eta_p^2 = 0.16$ and 0.26, respectively) and the sham tDCS session (both $p < 0.001$, $\eta_p^2 = 0.31$ and 0.58, respectively). In contrast, pain-related anxiety was not significantly altered by WM for either the 0-back or 2-back tasks in either the anodal or sham tDCS sessions (all $p > 0.2$, $\eta_p^2 \leq 0.09$). Regarding spinal nociceptive activity, NFR amplitude was not significantly altered by WM (all $p > 0.12$, $\eta_p^2 \leq 0.11$) except for the 0-back task of the sham condition in which it was decreased ($p = 0.001$, $\eta^2 = 0.29$).

Taken together, these results confirm that WM performance was not altered by the task-irrelevant painful stimuli. In addition, engagement of WM produced the expected decrease in pain perception, indicative of top–down regulation of pain by cognitive processes.

Table 1. Manipulation checks.

Measures	*n*-back task conditions				
	0-back	2-back	Pain	0-back with pain	2-back with pain
Pre-anodal tDCS					
RT (ms)	468.85 ± 24.12	399.68 ± 30.35		467.05 ± 12.82	403.66 ± 15.86
RA (%)	89 ± 2	83 ± 3		93 ± 1	83 ± 2
Pain ratings (0–100)	–	–	36.20 ± 2.02	32.59 ± 2.24	29.76 ± 2.24
Pain-related anxiety (0–100)	–	–	19.89 ± 3.35	17.31 ± 2.92	20.50 ± 3.49
NFR (Z score)	–	–	0.24 ± 0.11	0.06 ± 0.07	0.19 ± 0.10
Pre-Sham tDCS					
RT (ms)	473.29 ± 26.44	415.85 ± 27.06	–	453.18 ± 10.19	410.28 ± 17.47
RA (%)	89 ± 2	82 ± 2	–	94 ± 1	83 ± 2
Pain ratings (0–100)	–	–	36.03 ± 2.02	31.83 ± 2.48	29.76 ± 2.24
Pain-related anxiety (0–100)	–	–	18.26 ± 3.35	14.60 ± 2.80	16.19 ± 2.99
NFR (Z-score)	–	–	0.43 ± 0.09	− 0.04 ± 0.06	0.10 ± 0.08

Values in table are presented as the mean ± standard error of the mean tDCS, Transcranial direct current stimulation; RT, response time; RA, response accuracy; NFR, nociceptive flexion reflex

3.2 Effects of anodal tDCS

3.2.1 Working memory

Anodal tDCS significantly reduced RT in the 2-back task with or without pain compared with the respective pre-tDCS baseline values (both $p < 0.01$, $\eta_p^2 = 0.25$ and 0.32, respectively; see **Figure 8**a), while no difference was observed for the 0-back task with or without pain compared with their respective pre-tDCS baseline values (both $p > 0.5$, $\eta_p^2 = 0.06$ and < 0.01, respectively; see **Figure 8**a). In addition, no significant effect was produced by sham tDCS for either task, with or without pain (all $p > 0.4$, all $\eta_p^2 < 0.09$; see **Figure 8**b). Consistent with the reduction of RT, RA tended to improve with anodal tDCS in the 2-back with pain task compared with its pre-tDCS baseline value ($p = 0.057$, $\eta_p^2 = 0.20$), but no effect was observed for the other tasks (all $p > 0.4$, all $\eta^2 \leq 0.06$). In contrast, the sham tDCS did not produce any significant change in RA for any task compared with the respective pre-tDCS baseline values (all $p > 0.3$, all $\eta_p^2 \leq 0.06$; see **Figure 8**c, d). The between-session comparisons for RT and RA revealed no significant difference between anodal and sham tDCS (all $p' > 0.4$, $\eta_p^2 < 0.07$).

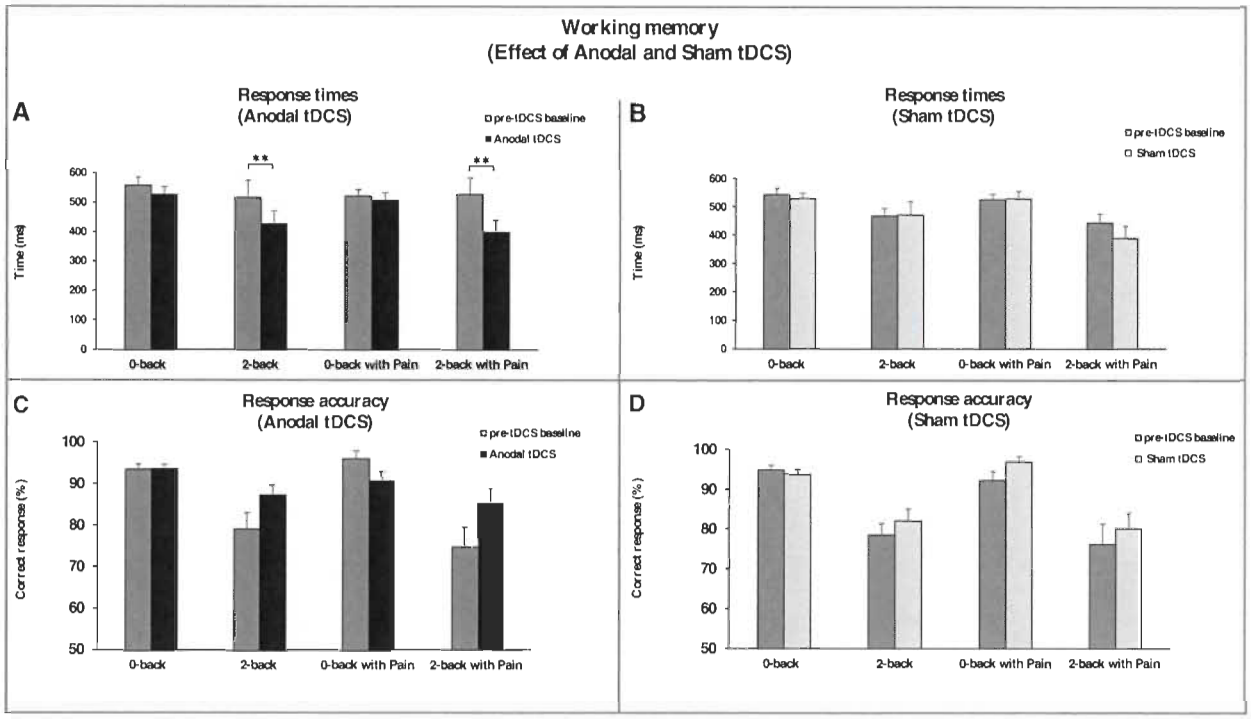

Figure 8. Effect of tDCS on working memory (WM).

a Reaction times (RT) during anodal tDCS. Anodal tDCS significantly reduced RT in the 2-back task with or without pain, compared with pre-tDCS baseline values, while no difference was observed for the 0-back task with or without pain compared with pre-tDCS baseline values (both $p > 0.5$). **b** RT during sham tDCS. No significant effect was produced by sham tDCS for either task, with or without pain (all $p > 0.4$). **c** Response accuracy (RA) during anodal tDCS. Consistent with the reduction of RT, RA tended to improve with anodal tDCS in the 2-back with pain task compared with the pre-tDCS baseline value ($p = 0.057$), but no effect was observed for the other tasks (all $p > 0.4$). **d** RA during sham tDCS. Sham tDCS did not produce any significant change in RA for any task compared with their respective pre-tDCS baseline values (all $p > 0.3$). Error bars Standard error of the mean (SEM). Double asterisks indicate significant difference at $p \leq 0.01$

3.2.2 Pain ratings

Anodal tDCS marginally improved pain inhibition by WM in the 2-back with pain task compared with its pre-tDCS baseline value ($p = 0.052$, $\eta^2 = 0.16$; see Fig. 4a). In contrast, pain and pain inhibition by WM in the 0-back task were not significantly different from their respective pre-tDCS baseline values (both $p > 0.2$, $\eta^2 = 0.05$ and 0.11, respectively; see **Figure 9**a). Also, sham tDCS produced no significant change in pain intensity for any of the three tasks (all $p > 0.2$, $\eta^2 = 0.13$, 0.10 and 0.01, respectively; see **Figure 9**b). The between-session comparisons revealed no significant difference between anodal and sham tDCS (all $p > 0.3$, $\eta_p^2 \leq 0.03$).

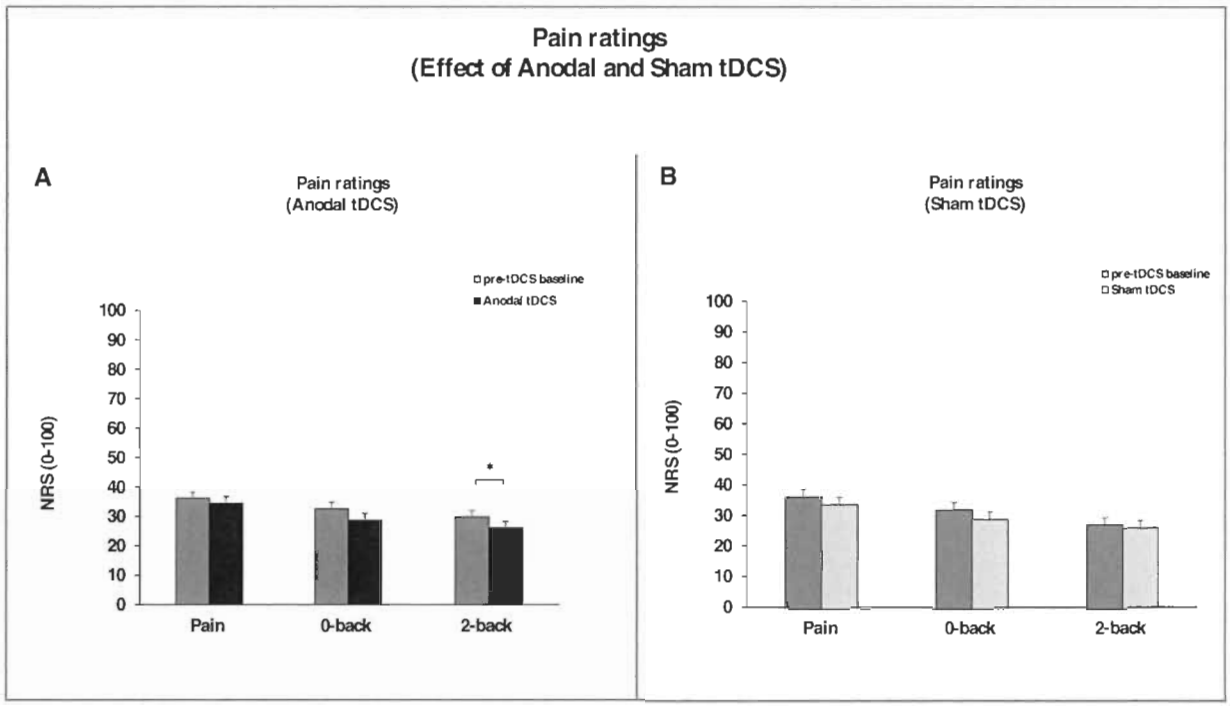

Figure 9. Effect of tDCS on pain ratings (NRS: 0–100).

a Pain ratings during anodal tDCS. Anodal tDCS marginally improved pain inhibition by WM in the 2-back with pain task compared with its pre-tDCS baseline value. In contrast, pain and pain inhibition by WM in the 0-back task were not significantly different from their respective pre-tDCS baseline values (both $p > 0.2$). **b** Pain ratings during sham tDCS. Sham tDCS produced no significant change in pain intensity for any of the three tasks (all $p > 0.2$). Error bars SEM. Single asterisk indicates significant difference at $p = 0.052$

3.2.3 Pain-related anxiety ratings

Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly altered by anodal tDCS compared with their respective pre-tDCS baseline values (all $p > 0.1$, $\eta_p^2 = 0.01$, 0.12 and 0.13, respectively; see **Figure 10**a). Similar results were

observed for the sham tDCS session (all $p > 0.3$, $\eta_p^2 = 0.08$, 0.08 and 0.02, respectively; see **Figure 10**b).

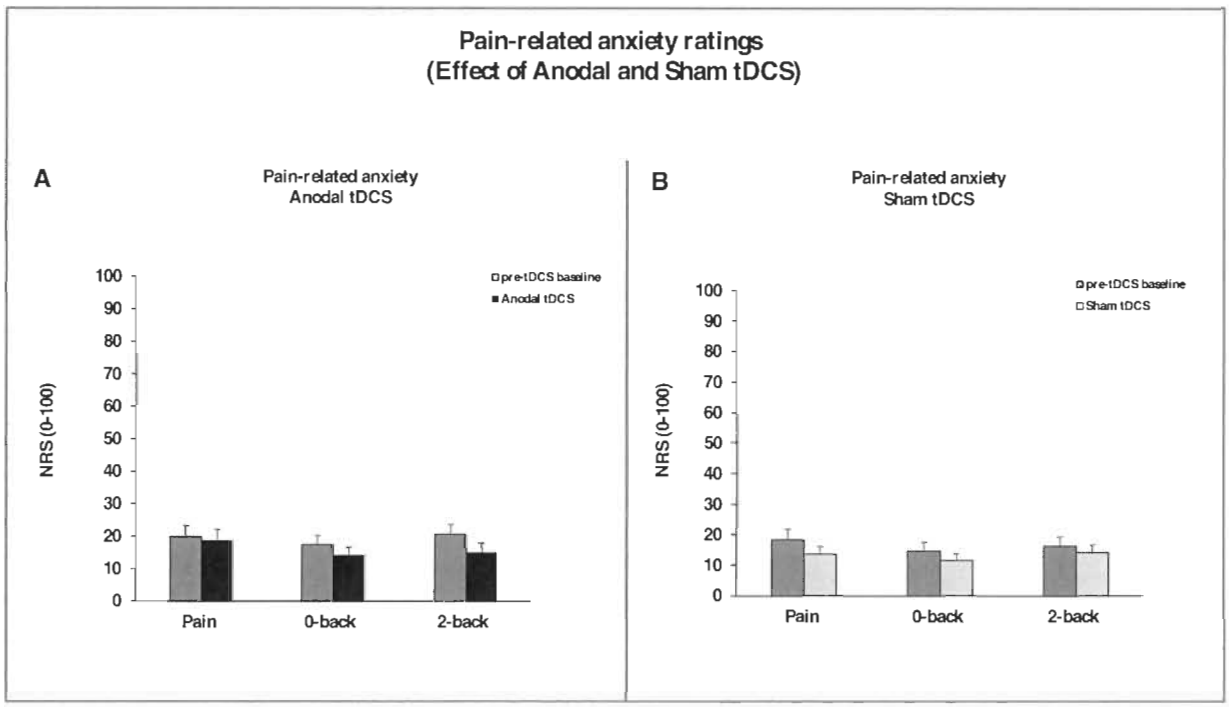

Figure 10. Effect of tDCS on pain-related anxiety.

a Pain-related anxiety during anodal tDCS. Pain-related anxiety and the inhibition of pain related anxiety by WM were not significantly modulated by anodal tDCS compared with their respective pre-tDCS baseline values (all $p > 0.1$). **b** Pain-related anxiety during sham tDCS. Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly modulated by sham tDCS compared with their respective pre-tDCS baseline values (all $p > 0.3$). Error bars SEM

3.2.4 NFR amplitude

NFR amplitude was significantly decreased during anodal tDCS compared with the pre-tDCS baseline value ($p = 0.04$, $\eta_p^2 = 0.17$; see **Figure 11**a). NFR inhibition by WM in the 0-back with pain and the 2-back with pain tasks were not significantly changed during anodal tDCS, although it tended to decrease compared with the respective pre-tDCS baseline ($p = 0.13$, $\eta_p^2 = 0.13$; see **Figure 11**b).

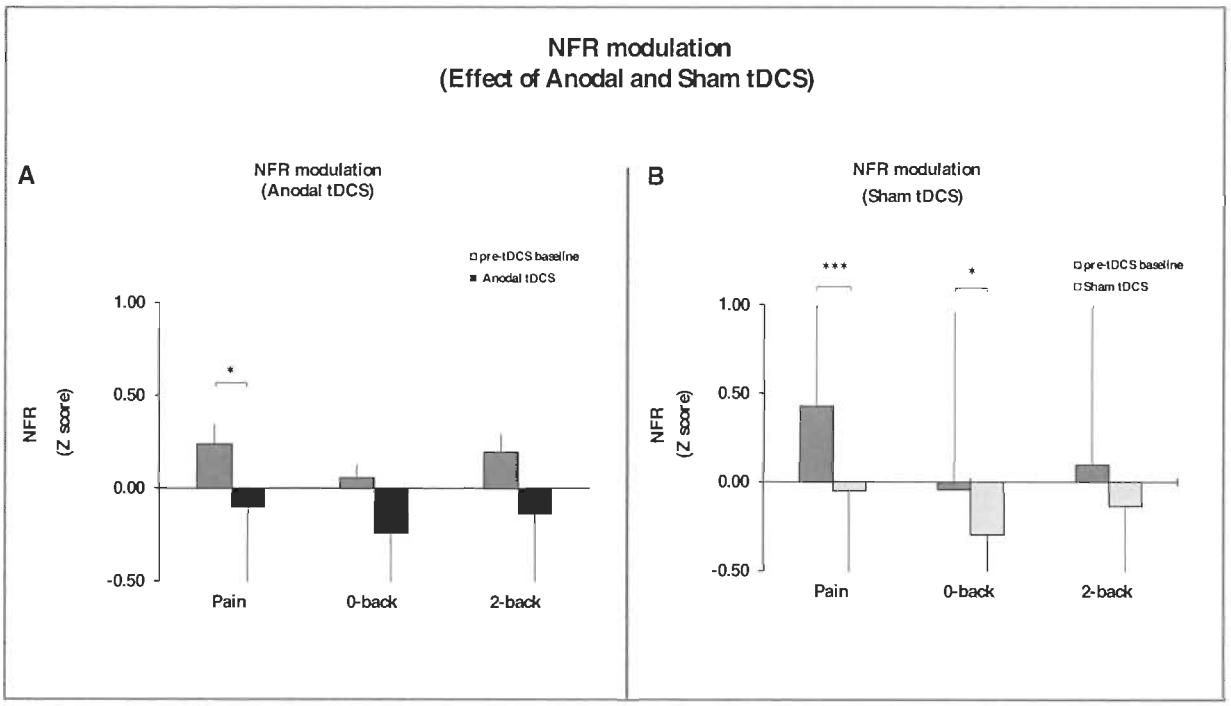

Figure 11. Effect of tDCS on nociceptive flexion reflex (NFR) amplitude.

a NFR modulation during anodal tDCS. NFR amplitude was significantly decreased during anodal tDCS compared with the pre-tDCS baseline value. NFR inhibition by WM in the 0-back with pain and the 2-back with pain tasks was not significantly changed by anodal tDCS, although

it tended to decrease compared with their respective pre-tDCS baseline values ($p = 0.067$ and $p = 0.057$, respectively). **b** NFR modulation during sham tDCS. NFR amplitude was significantly decreased during sham tDCS compared with the pre-tDCS baseline value while inhibition of NFR by WM was significantly greater than the pre-tDCS baseline value in the 0-back with pain task ($p = 0.036$) but in not the 2-back with pain task ($p = 0.13$). Error bars SEM. Single and triple asterisks indicate significant difference at $p < 0.05$ and $p < 0.001$, respectively

4. Discussion

The novel finding of this study is that pain inhibition by WM was enhanced by anodal tDCS of the left DLPFC, especially when WM engagement was stronger (2-back task). In contrast, pain perception was unchanged by anodal tDCS when painful stimuli were administered alone without the concurrent cognitive task. In addition, anodal tDCS improved WM but not NFR inhibition by WM, suggesting that anodal tDCS enhances pain inhibition by improving WM but not by increasing descending inhibition of spinal nociceptive activity.

4.1 Enhancement of WM and pain inhibition by tDCS

To have effective attentional control during pain perception, both the disengagement of attention from pain stimuli and the direction of attention to task-related information are essential (Crombez et al., 1998; Legrain, 2011a; Legrain et al., 2009; Oliveira et al., 2013). In order to test the specific inhibitory effect of WM engagement on pain perception, we used a modified n-back task with different WM loads (0-back and 2-back) (Legrain et al., 2013;

Legrain et al., 2011b). We compared conditions in which the n-back task was performed with or without painful distracters. To make painful distracters more salient and novel, they were applied rarely and randomly among frequent non painful stimuli (Legrain et al., 2013; Legrain et al., 2011b). Moreover, to determine the specific effect of anodal tDCS compared with sham tDCS and to control non-specific between-session effects, the experimental protocol was performed twice during each session, once as pre-tDCS baseline and once during tDCS. This allowed a within-session assessment of anodal tDCS and sham tDCS effects.

During the n-back task, mean RT was decreased during anodal tDCS over the left DLPFC. This effect was particularly observed in the high WM load condition (2-back task), while no effect was observed in the low WM load condition (0-back task). These results are consistent with improvement of WM by anodal tDCS of the left DLPFC (Andrews et al., 2011b; Brunoni et al., 2014; Hill et al., 2016; Kuo et al., 2012; Mariano et al., 2016; Mylius et al., 2012b; Wolkenstein et al., 2013) and with involvement of the DLPFC in the central executive system of WM (Awh et al., 2006; D'Esposito et al., 2000; Duncan, 2001; Lavie et al., 2006; Lavie et al., 2004; Legrain et al., 2009; Levy et al., 2000; Wager et al., 2014; Wolkenstein et al., 2013). They also extend these findings by showing that this WM improvement may contribute to the enhancement of pain inhibition. Indeed, pain inhibition by WM was enhanced by anodal tDCS in the high WM load condition. In contrast, pain perception was not affected by anodal tDCS when there was no engagement of WM (no n-back task). This suggests that in the present conditions, anodal tDCS of the left DLFPC may produce indirect effects on pain inhibition, through cognitive processes, without affecting pain perception directly. The present study also provides novel findings showing that increased pain inhibition by WM during tDCS

is not associated with significant inhibition of the NFR. This suggests that tDCS effects on pain inhibition by WM are mediated by supraspinal processes independent of descending pain inhibition processes.

TDCS neuromodulation may affect various brain networks depending on the positioning of stimulating electrodes and on the state of the stimulated network (Miniussi et al., 2013; Paulus, 2011). As a result, the outcome of the stimulation protocol depends on task characteristics, including WM load, as well as the state of the neural network (Miniussi et al., 2013; Roe et al., 2016). Coherent with this idea, some tDCS studies indicate that the effects of anodal tDCS are affected by task difficulty (Bikson et al., 2013; Jones et al., 2012). The availability of cognitive resources for optimal task performance is critical and the effects of tDCS may depend on increasing the availability of cognitive resources, especially when WM is highly loaded or saturated. In conditions with low WM load, cognitive resources are available as they are not monopolized by the task, so tDCS may not bring any gain in performance. This may explain some of the discrepancies observed between studies examining the effect of tDCS. The lack of tDCS effect may be due to the use of cognitive tasks that are not sufficiently demanding (Roe et al., 2016). Based on our findings, we propose that anodal tDCS of the DLPFC may be more effective during more demanding tasks, in accordance with the state-dependant or load-dependent effects reported earlier (Roe et al., 2016; Wu et al., 2014). This also leads to the inference that anodal tDCS of the DLPFC may be especially useful in clinical conditions in which WM and other cognitive functions are reduced.

4.2 Interactions between pain and WM

A nociceptive stimulus may be selected to prioritize a protective behavior in response to pain perception at the expense of task performance (Bingel et al., 2007a; Downar et al., 2003; Egeth et al., 1997; Escera et al., 2007; Knudsen, 2007; Legrain et al., 2009; Legrain, 2009; Yantis et al., 1990). Conversely, pain perception can be inhibited by cognitive processes if task execution is prioritized, in accordance with contextual demands (Bingel et al., 2007a; Hopfinger et al., 2006; Legrain et al., 2011a; Legrain et al., 2013; Legrain, 2002; Seminowicz et al., 2007b; Seminowicz et al., 2007c). In the present experiment, the protocol was designed to favour the execution of a cognitive task and the inhibition of pain. The comparison of working memory performance (response times) during pre-tDCS baseline showed no difference between conditions with or without pain. These results established that in our protocol, WM performance was not affected by salient painful distracters for either task difficulty (0-back or 2-back). WM engagement by rehearsing the features of visual targets was sufficient to avoid a bottom-up shift of attention to the salient painful distractors (Legrain et al., 2011a; Legrain et al., 2013; Legrain et al., 2011b; Legrain et al., 2009; Soto et al., 2005; Soto et al., 2008). In addition, accuracy in WM was consistent across all conditions. These findings were observed in previous pain studies (Coen et al., 2008; Legrain et al., 2011b; Legrain, 2011a). Indeed, nociceptive signals compete with other sensory signals for entering and further being processed by the attentional network (Berti et al., 2004; Legrain et al., 2009; Legrain, 2012; McCaul et al., 1985). This neural response to specific stimuli can be biased by stimulus saliency (bottom-up filter) (Egeth et al., 1997; Knudsen, 2007; Yantis et al., 1990) or by the relevance of stimuli for the task (top-down bias) (Folk et al., 1992; Hopfinger et al., 2006; Legrain, 2011a; Van Damme et al., 2010b). The

central executive component of WM that maintains task-relevant target features (attentional set) (Crombez et al., 1998; Legrain et al., 2009) and the maximal attentional load of WM capacity (Lavie et al., 2006; Lavie et al., 2004; Legrain et al., 2005a; SanMiguel et al., 2008) can be one source of bias (Baddeley, 2003; Legrain et al., 2011b; Legrain et al., 2009). Our results indicate that the present experimental paradigm is adapted to favour top-down inhibition of salient nociceptive signals. Moreover, 0-back and 2-back conditions produced the expected decrease in the pain ratings during pre-tDCS baseline. These results are consistent with the fact that RT were unaltered by pain and are also in line with results from previous studies (Bingel et al., 2007a; Buhle et al., 2010; Buhle et al., 2012; Coen et al., 2008). In summary, salient painful stimuli have the potential of disrupting WM but this is determined by the balance between bottom-up and top-down processes according to experimental conditions, including the working memory task (Buhle et al., 2010; Moore et al., 2013), the type and intensity of painful distractors as well as their novelty (Buhle et al., 2010; Legrain et al., 2011a; Legrain et al., 2013). In the present study, task performance was maintained and pain was inhibited in conditions involving both WM engagement and painful distracters. This allowed examining the effect of anodal tDCS of the DLPFC on pain inhibition by WM.

The present study also investigated the modulation of spinal nociceptive activity by WM with the NFR. NFR amplitude was reduced during low WM load (0-back) but not during high WM load (2-back) compared with the pain alone condition. The reduction of NFR amplitude suggests that descending pain inhibitory pathways were activated. However, the lack of inhibition in the high WM load condition is somewhat unexpected. Increased WM load and decreased pain perception should be associated with decreased NFR amplitude (Bushnell et al.,

1985; Eippert et al., 2009a; Sprenger et al., 2012), although dissociation between spinal activity and pain perception has been reported in previous studies (Bouhassira et al., 2003; Danziger et al., 1998b; Defrin et al., 2007a; Piche et al., 2009b; Terkelsen et al., 2004a). In the context of the present study, we postulate that the more demanding task produces a disinhibition of spinal nociceptive activity to maintain protective reflexes while WM shields cognition from nociceptive signals in the brain, in order to allow optimal task performance.

4.3 Limitations and future directions

Participants were asked to rate pain after each painful condition. This pain rating task in a way makes the painful stimuli relevant for participant's goals (Torta et al., 2017a). This could reduce inhibitory effects of WM by altering the balance between bottom-up and top-down processes. Also, although experimental conditions and sessions were counterbalanced between participants, the same participants performed all conditions in both sessions. Therefore, this has the potential of increasing the effect of sham tDCS and decreasing the relative effect of anodal tDCS compared with sham tDCS. However, this within-subject design is a fair compromise to avoid inter-subject variability, which may be larger than the within-subject counfound. However, this remains to be assessed in future studies. It could also be argued that within-subjects designs limit blinding of participants because they may feel a different sensation between sham and anodal sessions. However, participants were not aware that two different types of stimulation were used and they could feel electrical current in both sessions. Although the sensation may have been different, they received no instructions that may have induced a bias.

5. Conclusion

The results of our study are consistent with top–down suppression of pain by WM and with its improvement by anodal tDCS of left DLPFC, especially with more important WM engagement. In addition, anodal tDCS improved WM but not NFR inhibition by WM, implying that increased pain inhibition by WM improvement is independent of descending inhibition of spinal nociception.

Author contributions ZD contributed to all aspects of the research. SB contributed to data acquisition, analyses and interpretation. NR contributed to data acquisition and interpretation. IB contributed to experimental design, data interpretation and manuscript preparation. MP contributed to all aspects of the research and obtained funding for the study.

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Compliance with ethical standards

Ethical approval All experimental procedures conformed to the standards set by the latest

revision of the Declaration of Helsinki and were approved by the Research Ethics Board of Université du Québec à Trois-Rivières. All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice.

Conflict of interest Zoha Deldar reports no financial or other relation- ship that may lead to any conflict of interest. Nabi Rustamov reports no financial or other relationship that may lead to any conflict of interest. Suzie Bois reports no financial or other relationship that may lead to any conflict of interest. Isabelle Blanchette reports no financial or other relationship that may lead to any conflict of interest. Mathieu Piché reports no financial or other relationship that may lead to any conflict of interest.

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Chapter 3. Article of thesis

Improving working memory and pain inhibition in older persons using transcranial direct current stimulation

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Running title: Improving cognition and pain with neuromodulation

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Abstract

The aim of the present study was to examine whether transcranial Direct Current Stimulation (tDCS) could enhance working memory and pain inhibition in older persons. Fifteen volunteers (7 women, 8 men; mean±SD: 64±4.4 y.o.) participated in two tDCS sessions during which an n-back task was performed with two levels of working memory load, while painful stimulation was delivered at the ankle. The experiment included five within-subject counterbalanced conditions (pain alone and 0-back or 2- back with or without pain) performed twice during each session. Compared with the pre-tDCS baseline, anodal tDCS decreased response times and improved pain inhibition by working memory in the 2-back condition ($p < 0.01$), but not in the 0-back or pain alone conditions, while sham tDCS produced no effect (all $p > 0.3$). These results indicate that working memory and pain inhibition can be improved by tDCS in older persons.

1. Introduction

Recent empirical and theoretical work highlight the important links between pain and cognitive processes, notably attention. The neurocognitive model of attention to pain (Legrain et al., 2009a) describes two modes of attentional selection: bottom-up capture of attention by nociceptive stimuli and top-down attentional modulation of pain. In this model, attention allocation to nociceptive stimuli is affected by the trade-off between bottom-up and top- down processes. Bottom-up processes give nociceptive stimuli, which are intrinsically salient, stronger neuronal representation, leading to involuntary capture of attention. However, this bottom-up attentional capture can be modulated by top-down processes which are determined by cognitive goals represented in the WM.

According to this model, an effective task to reduce attentional capture by pain should be effortful and involve WM engagement. Consistent with this, the more the cognitive task is demanding, the more nociceptive processes will be inhibited, due to limited cognitive resources to be shared between bottom-up and top-down processes. Also, inhibition of nociceptive processing by top-down processes must be supported by WM, which preserves goal priorities and may shield cognition against nociception. While there is empirical evidence to support this prediction of the model in younger adults, this has not yet been investigated in aging, a variable related to pain in multiple ways.

Aging is associated with several physiological changes that affect global functioning, daily activity and quality of life. For instance, cognitive functions progressively decline during

normal aging, as evidenced by decreased episodic memory (Moscovitch and Winocur, 1995), attentional resources (Brink and McDowd, 1999), cognitive inhibition (Spieler et al., 1996) as well as working memory (WM) performance (Bopp and Verhaeghen, 2005; Borella et al., 2008; Darowski et al., 2008; De Beni and Palladino, 2004; Fabiani, 2012). Besides, pain conditions commonly occur and persist in the population over 40 years old, with a prevalence of chronic pain over 25% (Frondini et al., 2007; Mansfield et al., 2016). Whether the occurrence of cognitive decline and pain conditions are interrelated is still not clear, but interactions were shown between cognitive performance, pain sensitivity and age (Oosterman et al., 2013). Moreover, a correlational study showed that reduced pain inhibition is associated with reduced cognitive inhibition in older persons (Marouf et al., 2014). In addition, normal aging is associated with a decreased ability to suppress the processing of distracters. For example, decreased ability to inhibit distracting information when performing a cognitive task mediates age-related effects on WM performance (Darowski et al., 2008; Lustig et al., 2001). As a source of distracting information, pain may decrease cognitive task performance. This may be especially acute in older persons, who may show a greater alteration of cognitive functions. In turn, this alteration of cognitive functions, which results in decreased ability to inhibit distracters such as pain, may worsen pain symptoms and lead to a vicious circle with important impacts. Consistent with this idea, overall cognitive performance is lower in patients with chronic pain, relative to controls, and this is observed particularly in older patients (Moriarty et al., 2017).

Indeed, effective cognitive control during pain perception depends on the disengagement of attention from task-irrelevant pain signals towards the processing of task-relevant information (Legrain et al., 2011, 2013). WM allows these processes to take place, while inhibiting

nociceptive brain activity and pain perception (Legrain et al., 2009a). Accordingly, reduced WM in older persons may decrease top-down inhibition of nociceptive activity and pain (Gazzaley et al., 2005). Thus interventions aimed at improving WM, pain inhibition or pain inhibition by WM are needed. In line with this idea, results from a recent study suggest that anodal transcranial Direct Current Stimulation (tDCS) of the left dorsolateral prefrontal cortex (DLPFC) enhances pain inhibition by improving WM in a sample of young healthy volunteers (Deldar et al., 2018). This type of intervention could present an interesting therapeutic avenue to address the age-related decline in WM performance and pain regulation.

The aim of the present study was to investigate whether anodal tDCS of the DLPFC could improve pain inhibition by WM in older persons. We hypothesized that anodal tDCS of the left DLPFC would improve WM performance, which in turn, would improve top- down pain inhibition during a cognitive task involving WM. Using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission, we also examined whether descending inhibitory pathways contribute to the enhancement of pain inhibition by WM.

2. Material and methods

2.1. Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of Université du Québec à Trois-Rivières. All participants gave written informed consent, acknowledging their

right to withdraw from the experiment with- out prejudice and received a compensation of $50 for their travel expenses, time and commitment.

2.2. Participants

Fifteen healthy volunteers (7 women and 8 men; range 55–71 years old; mean ± SD: 64 ± 4.41) were recruited by advertisements on the campus of Université du Québec à Trois-Rivières and through local associations for seniors. Participants were included if they were between 55 and 75 years old with normal or corrected-to- normal vision. They were excluded if they had taken any medication affecting the nervous system or pain perception within two weeks before the experiment, including antihypertensives, pain killers, anxiolytics, antidepressants and other psychotropic medication and if they had a history of acute or chronic pain, suffered from acute or chronic neurological illness, heart disease, metabolic disorders, vascular disorders or if they were diagnosed with a psychiatric disorder. They were also asked to abstain from consuming alcohol at least 1 day before experimentation. Five participants could not complete experimental procedures; in two participants, the NFR could not be evoked at a stimulus intensity that was tolerable for the participant in the context of this study. The other participants could not perform the n-back task. Therefore, data from these five participants were not collected, leaving a sample of 15 participants.

2.3. Experimental design

This experiment is based on a within-subject double-blind sham-controlled design to determine the effect of a single anodal tDCS session applied over the left DLPFC on WM and pain inhibition by WM, as reported in our previous study (Deldar et al., 2018). To elicit WM engagement, a modified n-back task was used. The task consisted in colour discrimination of blue and yellow squares. In order to obtain two different levels of WM load, the n-back task was either 0-back, in which participants responded by reporting the colour of the current stimulus, or 2-back, in which participants responded by reporting the colour of the stimulus presented two trials earlier. Painful stimuli were delivered alone or concurrently to the n-back task to test the interaction between WM and pain. In these conditions, sixty electrical stimuli were delivered randomly, among which ten stimuli were painful and 50 stimuli were non-painful. This increases painful stimulus saliency. Thus, the experiment included five within-subject counterbalanced conditions (pain alone and 0-back or 2-back with or without pain) performed twice during each session.

2.4. Electrical stimulation

Transcutaneous electrical stimulation (trains of 10 x 1 ms pulses at 333 Hz) was delivered with two isolated DS7 A constant cur- rent stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA, USA). Stimulators were controlled by a script running in a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). The

degreased skin over the retromalleolar path of the right sural nerve was stimulated by two adjacent pairs of custom-made surface electrodes (1 cm2; 2 cm inter-electrode distance) for the painful and tactile stimuli, respectively. For the painful stimulus, the NFR threshold was determined using the staircase method (Ladouceur et al., 2018, 2012; Piche et al., 2011). For the tactile stimulus, the detection threshold was determined as the first stimulus intensity that produced a tactile sensation under the electrodes. The painful and tactile stimuli were always delivered with the same pair of electrodes. In both sessions, stimulus intensity was adjusted individually to 120% of the NFR threshold for painful stimulation and to 150% of the detection threshold for non-painful stimulation.

2.5. Nociceptive flexion reflex measure and analysis

Electromyography (EMG) of the short head of the biceps femoris was recorded with a pair of surface electrodes (EL-508, Biopac Systems, Inc., Goleta, CA, USA). Signal was amplified 2000 times, band pass filtered (10–500 Hz), sampled at 1000 Hz (Biopac Systems, Inc., Goleta, CA, USA) and stored on a personal computer for off-line analyses. The raw EMG recordings were full wave rectified and the resulting signal was used to quantify the amplitude of NFR to each shock by extracting the integral value between 90 and 180 ms after stimulus onset. This amplitude was standardized using a within- subject z-transformation. For group analyses, the mean response to 10 painful stimuli was calculated for each condition.

2.6. Pain and pain-related anxiety ratings

Participants verbally rated pain intensity and pain-related anxiety using numerical rating scales (NRS) with two anchors on the left and right extremities (0, no pain/anxiety and 100, extreme pain/anxiety). These scales were displayed horizontally on a computer screen after each condition.

2.7. Transcranial direct current stimulation

A direct current of 2mA was generated by a battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) and delivered continuously using a pair of rubber electrodes (35 cm2 surface) covered by conductive sponges moistened with saline. To enhance the activity of the left DLPFC, the anodal electrode was placed on the scalp over the F3 site, according to the international 10–20 system of electrode placement. The cathode was placed over the right deltoid muscle to make sure that tDCS effects were due only to anodal stimulation (Wolkenstein and Plewnia, 2013). During the first 30 s of stimulation, the current was ramped up to 2 mA and then delivered for 22 min. The first 3 min allowed participants to get used to tDCS before beginning the task. At the end of stimulation, the current was ramped down to 0 mA over 30 s. For the sham stimulation, electrodes were placed in the same positions but the current was only applied for 40 s. Pre-defined codes assigned to either sham or anodal stimulation were used to start the stimulator. These codes allowed for a double-blind study design. The order of tDCS and sham stimulation was counterbalanced across participants with a one-week inter-session interval.

2.8. Psychometric assessment

Participants completed validated questionnaires. Anxiety was assessed using the Spielberger State-Trait Anxiety Inventory (STAI- Y) in its original English or validated French version (Vigneau, 2009), depending on participant's mother language. Pain catastrophizing was evaluated using the French or English version of the Pain Catastrophizing Scale (PCS) (French et al., 2005). To measure how participants pay attention to pain in daily life, they also completed the pain vigilance and awareness questionnaire (PVAQ) (Roelofs et al., 2003). To measure individual differences in attentional control, they completed the Attentional Control Scale (ACS) (Derryberry and Reed, 2002). Depressive symptoms were measured using the French or English version of the Geriatric Depression Scale (GDS) (Yesavage et al., 1982). Cognitive impairment was evaluated using the Montreal Cognitive Assessment (Nasreddine et al., 2005).

2.9. Cognitive task

A modified n-back task was used in which the participant had to discriminate between blue and yellow squares with two levels of WM load (0-back and 2-back conditions) (Deldar et al., 2018). In the 0-back condition, participants discriminated the colour of the current stimulus directly after its presentation. In the 2-back condition, they responded to the stimulus presented two trials before. WM performance was examined with response time (RT) and response accuracy (RA: percentage of correct responses). The mean RT was calculated for each condition by including RTs from each trial with a correct response. Trials defined as anticipated responses

(RT < 150 ms) or missed responses (RT > 1500 ms) were excluded from the mean RT calculation.

For conditions with electrical stimulation during the n-back task, one series of task-relevant stimuli (blue or yellow squares presented for 500 ms) was shortly preceded by a task-irrelevant electrical stimulation (non-painful: 200 ms before; painful: 300 ms before; see **Figure 12**). 83% of electrical stimuli were non-painful and 17% were painful, following the procedure described previously (Deldar et al., 2018). The inter-stimulus interval (ISI) between the onset of the electrical stimulus and the onset of task-relevant stim- ulus was either 220 ms for tactile trials and 300 ms for painful trials, in order to account for the conduction velocity of tactile and nociceptive fibres. The inter-trial interval (ITI) between the onsets of two consecutive task-relevant stimuli was 3000 ms.

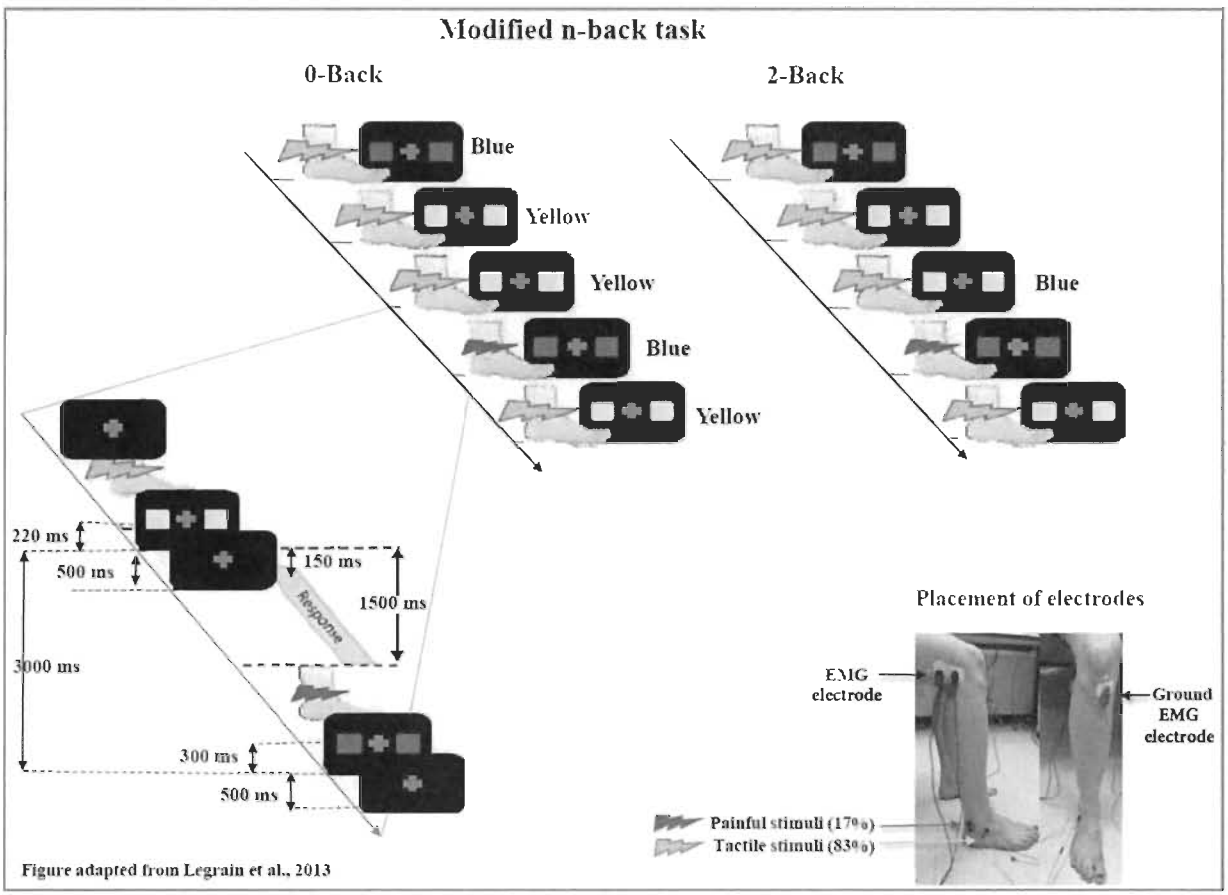

Figure 12. Modified n-back task.

Participants performed a modified n-back task in which they had to discriminate the colour of each visual stimulus, consisting in two blue or two yellow squares. In the 0-backcondition, they discriminated the colour of the current stimulus immediatly after its presentation. In the 2-back condition, they responded for the stimulus discriminated two trials before. The visual stimulus was preceded by a tactile stimulus in 83% of trials or by a painful stimulus in the remaining trials (17%). The bottom left panel indicates the sequential timings of stimuli in each trial. A fixation cross was presented at the center of the screen during the entire trial. Electrical stimuli were followed by a visual stimulus of 500 ms duration. The interval between the somatosensory and visual stimuli (ISI) was 220 ms for the tactile trials and 300 ms for the painful trials. Task

performance was measured in the time window running from 150 to 1500 ms after visual stimulus onset. The next trial began after the response with a fixed inter-trial interval (ITI) of 3000 ms. The placement of the electrodes for painful and tactile stimulation is illustrated at the bottom right of the figure. Two pairs of surface electrodes were placed adjacently on the path of the right sural nerve (painful stimulation) and on the anterior part of the right lateral malleolus (tactile stimulation). Electromyography (EMG) was recorded with a pair of surface electrodes from the short head of the biceps femoris with the ground placed on the medial aspect of the tibial tuberosity.

2.10. Experimental procedures

Participants completed two 180-minute sessions on separate days with a 1-week interval. All participants received anodal brain stimulation and sham stimulation; the order was counter-balanced across participants. The same protocol was carried out in both sessions. After individual adjustment of stimulus intensity for ankle stimulation, the tDCS electrodes were placed as described above and participants were familiarized with the n- back task. Familiarization included twenty trials for each condition, during which participants received feedback (correct or incorrect response) (Deldar et al., 2018). After this practice, the experimental protocol began with the pre-tDCS baseline conditions (pain alone and 0-back or 2-back with or without pain) followed by the same five conditions during tDCS (see **Figure 13**). Each condition included 60 trials. For the 0-back and 2-back conditions, the 60 trials were presented without any electrical stimulation. For the pain condition, the 60 trials included 50 tactile stimuli and 10 painful stimuli with- out the n-back task, as in our previous study (Deldar

et al., 2018). For the 0-back and 2-back with pain conditions, 50 trials of the n-back task were preceded by a tactile stimulus while 10 trials were pre- ceded by a painful stimulus. The order of the five conditions was counterbalanced between subjects but the same order was kept within-subject for the pre-tDCS baseline and tDCS conditions, as well as for both sessions (anodal and sham).

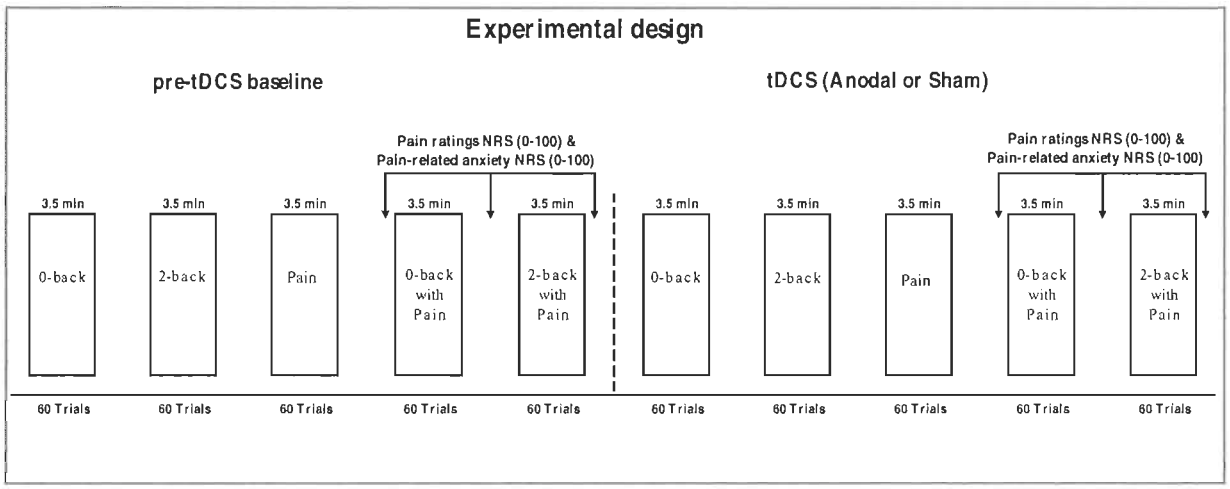

Figure 13. Experimental design.

The experimental protocol comprised five counterbalanced conditions, including 0-back, 2-back, pain, 0-back with pain and 2-back with pain. This experimental protocol was performed twice during each session, once to establish a pre-tDCS baseline and once during tDCS. The same order was used for the sham and anodal tDCS sessions fora given participant. The condition duration was 3.5 min and each condition contained 60 trials. Participants were instructed to rate pain and pain-related anxiety at the end of each condition comprising painful stimuli using a numerical rating scale (0–100).

2.11. Statistical analysis

Data analysis was conducted using Statistica v13.1 (Dell Inc., Tulsa, OK, USA). All results are expressed as mean ± SEM and statistical threshold was set to $p \leq 0.05$ (two-tailed). Distribution normality was confirmed using the Kolmogorov-Smirnov test and data was transformed (1/x) for variables which distribution deviated from normality (RT and RA). A priori hypotheses were tested with planned contrasts and the type I error rate was controlled for using the Bonferroni correction for multiple comparisons, based on the number of comparisons for each independent analysis. All reported p-values are therefore corrected for multiple comparisons for all variables, including RT, RA, pain, pain-related anxiety and NFR amplitude. Effect sizes are reported based on partial eta- squared ($\eta p2$).

3. Results

The sample included 15 participants. Results from the psychometric and pain assessments are reported in (**Table 2**).

Table 2. Characteristics of participants.

N = 15; 7 Females and 8 Males	Mean ± SEM (range)
Age (y.o.)	64 ± 4.41 (55-71)
Depressive symptoms (GDS) (0-30)	3.6 ± 0.8 (0-10)
Pain catastrophizing (PCS) (0-52)	13.7 ± 3.0 (0-37)
Pain vigilance and awareness (PVAQ) (0-80)	36.5 ± 2.4 (22-50)
Trait anxiety (STAI-Y) (0-80)	47.1 ± 0.7 (43-51)
State anxiety (STAI-Y) (0-80)	47.4 ± 0.7 (43-54)
Attentional control scale (ACS) (0-80)	48.9 ± 0.7 (44-53)
Cognitive function (MOCA) (0-30)	29.2 ± 0.4 (25-30)
Pain threshold (mA) for sham and anodal tDCS sessions	7.33 ± 1.33 (3-15)
Nociceptive flexion reflex threshold (mA) for sham and anodal tDCS sessions	8.8 ± 1.60 (3.6-18)

3.1. Interactions between pain and working memory

To examine the interactions between pain and WM, pre-tDCS baseline values averaged between sessions were compared between conditions to test whether pain distracters altered WM or whether WM engagement decreased the capture of attention by painful distracters (see **Table 3**). RT was significantly decreased when painful distracters occurred during the 0-back condition ($p = 0.032$, $\eta p2 = 0.35$) and marginally decreased during the 2-back condition ($p = 0.054$, $\eta p2 = 0.30$), while response accuracy was not affected by painful distracters either in the 0-back ($p = 0.8$, $\eta p2 < 0.01$) or 2-back ($p = 0.4$, $\eta p2 = 0.12$) conditions. Besides, pain ratings were significantly decreased by WM engagement in the 0-back ($p = 0.003$, $\eta p2 = 0.52$) and 2-back ($p = 0.006$, $\eta p2 = 0.48$) conditions. In contrast, pain-related anxiety ratings were not significantly decreased by WM engagement in the 0-back condition ($p = 0.8$, $\eta p2 = 0.05$) and

were significantly increased in the 2-back condition ($p = 0.04$, $\eta p2 = 0.34$). As for spinal nociceptive activity, NFR amplitude was not significantly altered by WM engagement either in the 0-back ($p = 0.9$, $\eta p2 < 0.01$) or 2-back ($p = 0.6$, $\eta p2 = 0.07$) condition.

These results indicate that response times were faster when the 0-back and 2-back tasks were performed with painful distracters compared to the respective n-back task alone. In addition, pain perception was decreased when a WM task was performed (either the 0-back or the 2-back), compared with painful stimulation alone, confirming that the engagement of WM can reduce pain perception. In the following analyses, we examined whether anodal tDCS could improve WM performance and pain inhibition by WM engagement.

Table 3. Interactions between pain and working memory (pre-tDCS baseline values).

	0-back	2-back	Pain	0-back with pain	2-back with pain
Response time (ms)	548.8 ± 17.8	491.01 ± 31.8	-	521.1 ± 15.2	484.32 ± 32.6
Response accuracy (%)	94 ± 0.9	78.7 ± 2.4	-	94 ± 1.5	75.3 ± 3.5
Pain ratings (0-100)	-	-	32.5 ± 4.1	26.4 ± 3.3	24.8 ± 2.4
Pain-related anxiety ratings (0-100)	-	-	10.4 ± 2.6	9.2 ± 1.9	18.4 ± 3.4
Nociceptive flexion reflex amplitude (T-score)	-	-	49.3 ± 1.3	49.5 ± 1.0	51.3 ± 1.0

3.2. Effects of transcranial direct current stimulation

3.2.1. Working memory

Compared with pre-tDCS baseline values, anodal tDCS significantly reduced RT in the 2-back condition, with or without pain (both $p < 0.01$, $\eta p2 = 0.58$ and 0.52, respectively; see **Figure 14**A) while no significant effect was observed for the 0-back condition, with or without pain (both $p > 0.3$, $\eta p2 = 0.23$ and 0.10, respectively; see **Figure 14**A). Besides, no significant

effect was produced by sham tDCS in the 0-back and 2-back conditions, with or without pain (all $p > 0.3$, all $\eta p2 < 0.22$; see **Figure 14**B). However, anodal tDCS effects were not significantly greater than those produced by sham tDCS (all $p > 0.3$, all $\eta p2 < 0.12$). As for RA, no significant change was produced for any condition by either anodal or sham tDCS (all $p > 0.1$, all $\eta p2 < 0.34$; see **Figure 14**C and **Figure 14**D).

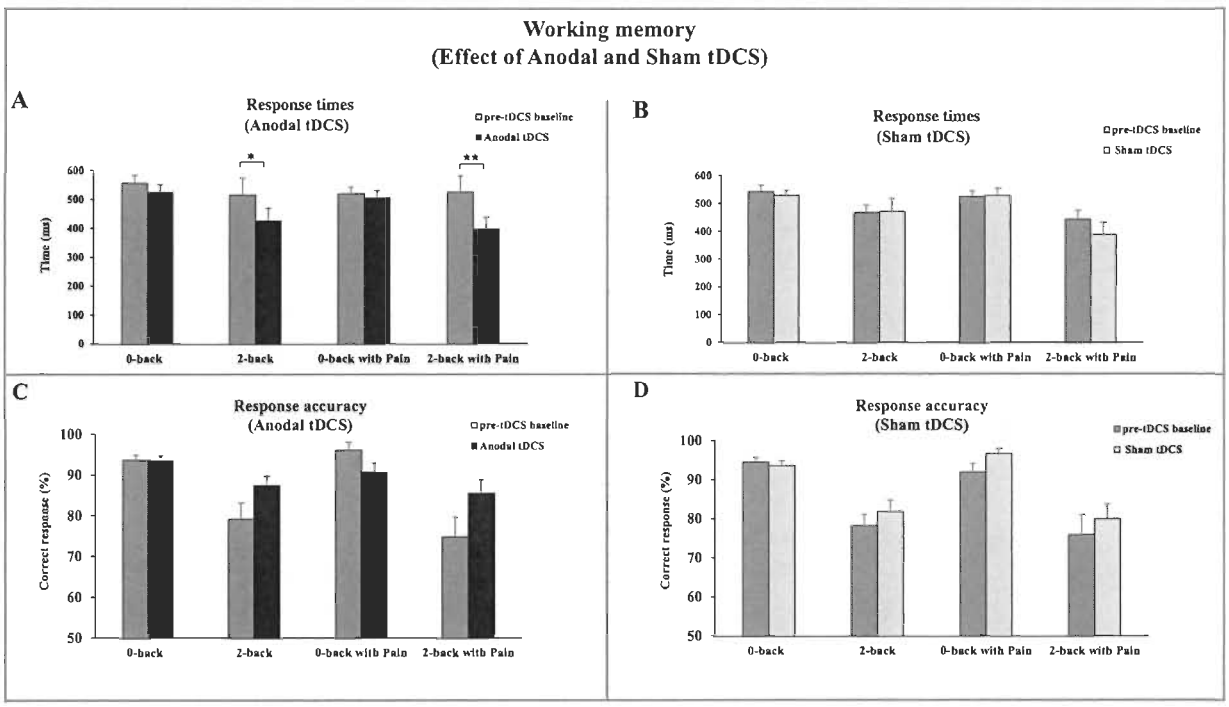

Figure 14. Effect of tDCS on working memory.

A) Anodal tDCS significantly reduced response times (RT) in the 2-back task with or without pain, compared with pre-tDCS baseline (both $p < 0.01$), while no difference was observed for the 0-back task with or without pain compared with pre-tDCS baseline (both $p > 0.3$). **B)** No significant effect was produced by sham tDCS for either task, with or without pain, compared with pre-tDCS baseline (all $p > 0.3$. **C)** No effect of anodal tDCS was observed on response accuracy (RA) for either task, with or without pain, compared with pre-tDCS baseline (all $p >$

0.1). **D)** Sham tDCS did not produce any significant change in response accuracy for any task compared with their respective pre-tDCS baseline (all $p > 0.1$). Error bars indicate standard error of the mean. $^{**}p \leq 0.01$.

3.2.2. Pain intensity

Anodal tDCS significantly improved pain inhibition by WM in the 2-back with pain condition compared with the pre-tDCS 2-back with pain condition ($p < 0.01$, $\eta p2 = 0.55$; see **Figure 15**A). In contrast, pain and pain inhibition by WM in the 0-back task were not significantly different compared with their respective pre-tDCS condition (both $p > 0.8$, $\eta p2 = 0.16$ and 0.01, respectively; see **Figure 15**A). Sham tDCS produced no significant change in pain intensity for any of the three conditions (all $p>0.9$, all $\eta p2<0.10$; see **Figure 15**B). However, anodal tDCS effects were not significantly greater than those produced by sham tDCS (all $p > 0.9$, all $\eta p2 <0.13$).

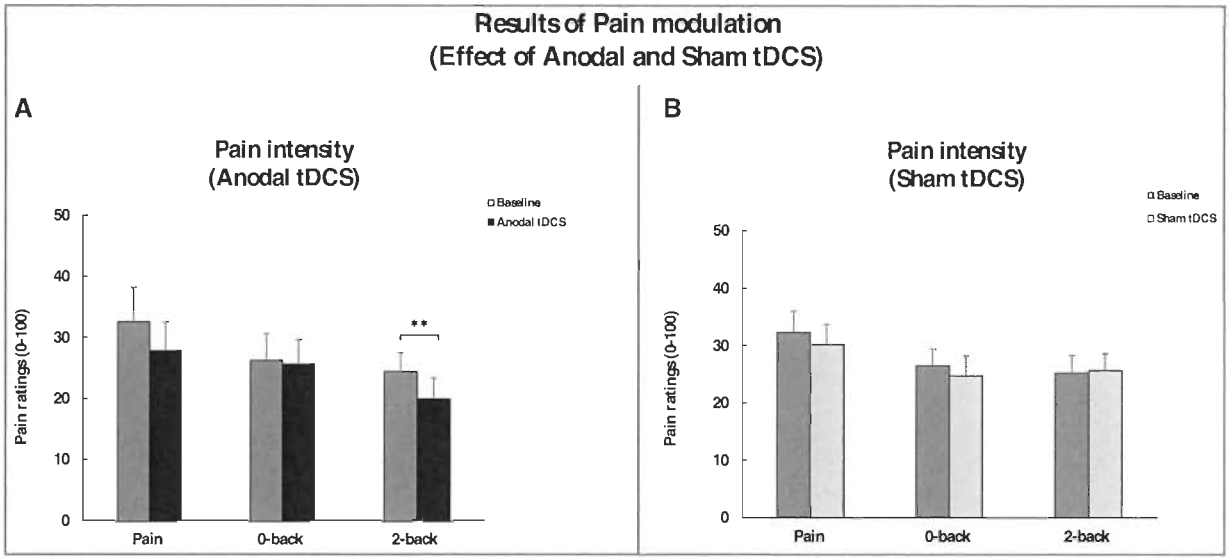

Figure 15. Effect of tDCS on pain intensity.

A) Anodal tDCS significantly increased pain inhibition by WM in the 2-back with pain task compared with pre-tDCS baseline ($p < 0.01$). In contrast, pain and pain inhibition by WM in the 0-back task were not significantly different compared with pre-tDCS baseline (both $p > 0.8$). **B)** Sham tDCS produced no significant change in pain intensity for any of the three tasks compared with pre-tDCS baseline (all $p > 0.9$). Error bars indicate standard error of the mean. $^{**}p \leq 0.01$.

3.2.3. Pain-related anxiety

Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly improved by anodal tDCS compared with their respective pre-tDCS condition (all $p > 0.1$, $\eta p2 = 0.09$. 0.01 and 0.38, respectively; see **Figure 16**A). Similar results were observed for the sham tDCS session (all $p > 0.9$, all $\eta p2 < 0.14$; see **Figure 16**B).

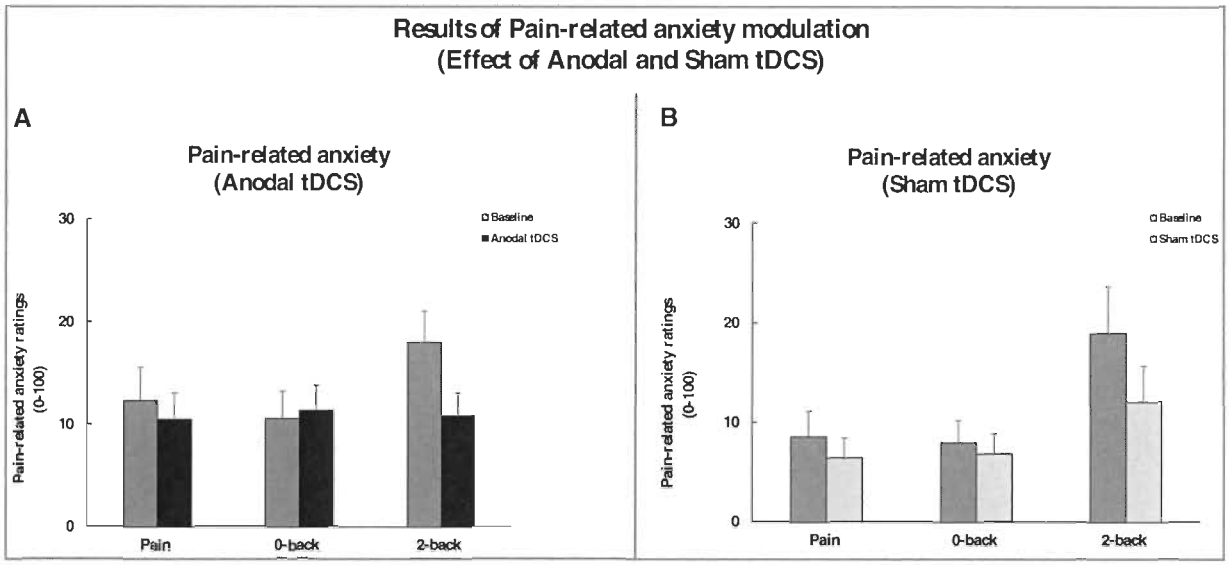

Figure 16. Effect of tDCS on pain-related anxiety.

A) Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly modulated by anodal tDCS compared with pre-tDCS baseline (all $p > 0.1$). **B)** Pain-related anxiety and the inhibition of pain-related anxiety by WM were not significantly modulated by sham tDCS compared with pre-tDCS baseline (all $p > 0.9$). Error bars indicate standard error of the mean.

3.2.4. Nociceptive flexion reflex

Figure 17 shows an individual example of NFR in each condition. As for group analyses, anodal tDCS produced no significant change in NFR amplitude for any of the three conditions (all $p>0.9$, all $\eta p2<0.13$; see **Figure 18**A). Similar results were observed for the sham tDCS session (all $p > 0.3$, $\eta p2 = 0.03$. 0.10 and 0.26, respectively; see **Figure 18**B).

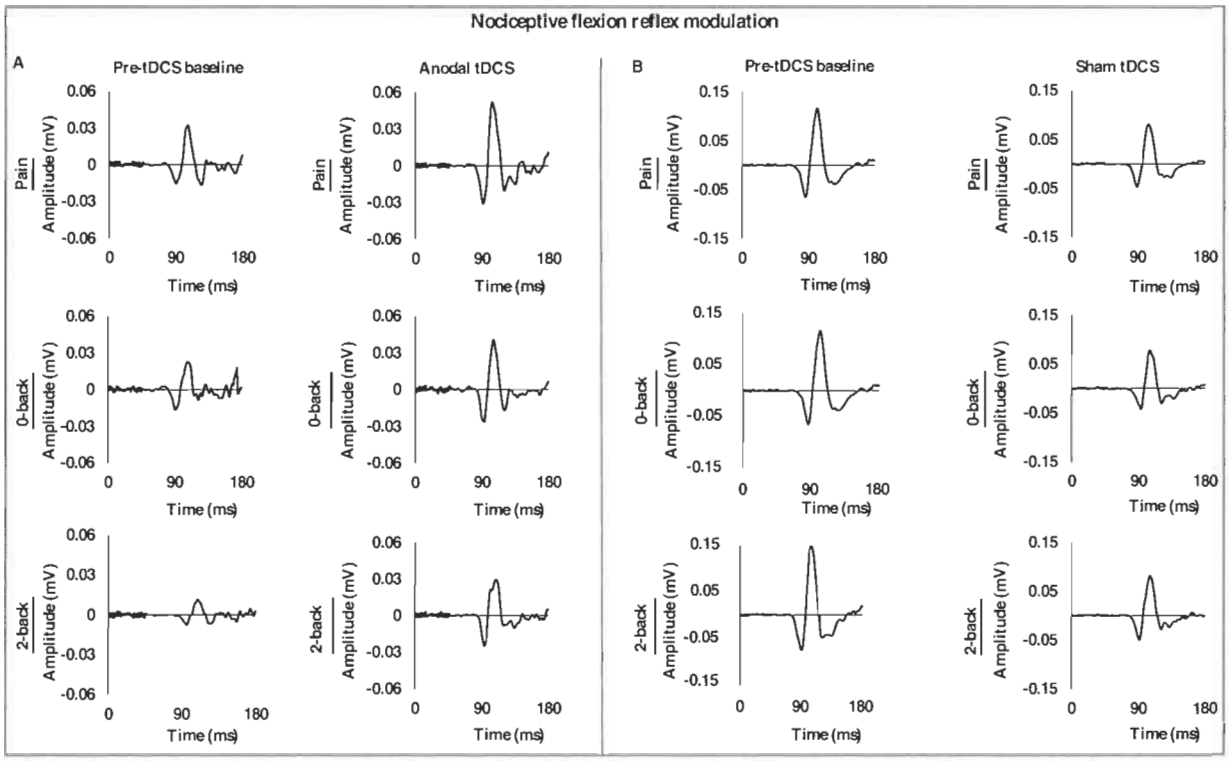

Figure 17. Individual example of the raw NFR traces in each condition.

A) Average NFR (10 trials) for one participant during pre-tDCS baseline and anodal tDCS in the three conditions (pain; 0-back; 2-back). B) Average NFR (10 trials) for one participant during pre-tDCS baseline and sham tDCS in the three conditions (pain; 0-back; 2-back). In line with group results, anodal tDCS did not improve NFR inhibition.

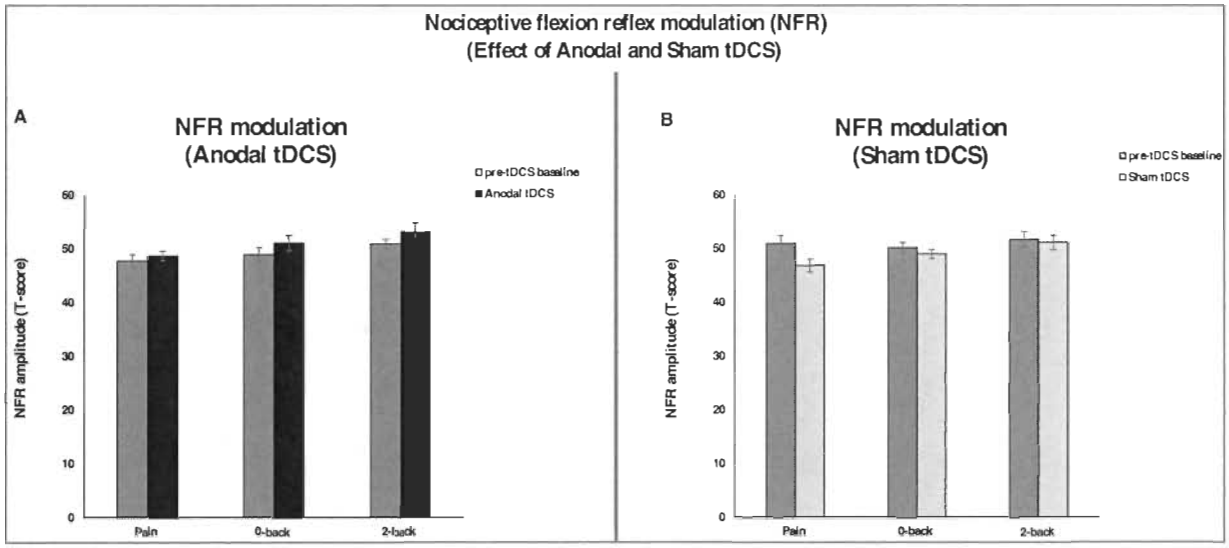

Figure 18. Effect of tDCS on NFR amplitude.

A) NFR amplitude was not significantly modulated by anodal tDCS compared with pre-tDCS baseline (all $p > 0.9$). **B)** NFR amplitude was not significantly modulated by sham tDCS compared with pre-tDCS baseline (all $p > 0.3$). Error bars indicate standard error of the mean.

4. Discussion

The novel finding of the present study conducted in older persons is that pain inhibition by WM engagement was enhanced by anodal tDCS in the high load WM condition (2-back task), while pain itself was not significantly decreased. This indicates that anodal tDCS can enhance pain inhibition by improving WM in healthy older persons.

4.1. Enhancement of working memory and pain inhibition by tDCS

In the present study, anodal tDCS over the left DLPFC decreased mean RTs during the n-back task. This effect was particularly observed in the high WM load conditions while no effect was observed in the low WM load conditions. These results of anodal tDCS on mean RTs replicate our previous findings obtained in younger participants with the same experimental paradigm (Deldar et al., 2018). A study also reported that ten sessions of cognitive training combined with 30 min of tDCS over of the pre- frontal cortex bilaterally improved accuracy in a verbal working memory task compared with sham tDCS, in older persons (mean age of 69.7 y.o.) (Park et al., 2014). Another study in which ten sessions of cognitive training combined with sham or anodal tDCS of the right prefrontal, parietal, or prefrontal/parietal cortex were performed reported that older persons (mean age 64.4 y.o.) showed WM improvement, in the anodal tDCS groups only, regardless of tDCS location.

In addition to WM performance, the present results indicate that anodal tDCS could improve pain inhibition by WM. This is also consistent with results from a previous study in young participants (Deldar et al., 2018). Although we suggest that pain inhibition was improved by an improvement of WM, we cannot exclude the possibility that both effects may be produced by independent processes. However, these hypoalgesic effects were observed only with high WM load (2-back task), while no effect was observed with the low WM load condition (0-back task). This suggests that anodal tDCS of the DLPFC may improve pain inhibition by WM but only when the WM task is sufficiently demanding, in accordance with previously described state-dependent or load-dependent effects of tDCS (Roe et al., 2016; Wu et al., 2014). In

addition, pain itself was not decreased by anodal tDCS in the present and in our previous study (Deldar et al., 2018), indicating that improvement of pain inhibition by WM with anodal tDCS relies on the interaction of WM with pain-related processes and not on a direct effect on pain-related processes. Also, the lack of significant change in NFR amplitude suggest that this interaction relies on a supraspinal mechanism that do not involve descending modulation.

4.2. Interactions between pain and cognition in older persons

The comparison of WM performance between conditions during pre-tDCS baseline showed that response times were shorter when the 0-back and 2-back tasks were performed with painful distracters compared with the same tasks without painful distracters. There may be experimental conditions or daily situations in which pain is prioritized, resulting in reduced cognitive performance. For instance, patients with fear of pain or with chronic pain may be hypervigilant to pain (Van Damme et al., 2010), which could bias attention towards pain processing at the expense of cognitive task execution. One possibility that should be considered to explain the improvement of WM by anodal tDCS is that anodal tDCS produces a sensation on the scalp that may increase alertness, possibly leading to an improvement in RT. However, this possibility is unlikely since the same sensation did not pro- duce a similar effect in the 0-back condition. In addition, it was reported that when participants prioritize a cognitive task, like the n-back task, RT are decreased (Erpelding et al., 2013). Pain was also decreased by the execution of the 0-back and 2-back tasks, indicating that attentional control was effective and that task execution was prioritized, resulting in reduced processing of painful distracters. Effective attentional control to execute a cognitive task in spite of painful distracters depends

on the disengagement of attention from pain and on the allocation of cognitive resources to maintain attention on the processing of task-relevant information (Legrain et al., 2009b). The present results indicate that WM maintenance of the visual targets of the n-back task helped to shift attention away from the painful stimulus.

4.3. Significance, future directions and limitations

Chronic pain conditions may advance with the age-related cognitive decline. Besides, pain is associated with changes in the brain that may worsen the cognitive decline observed in older adults. For instance, patients with chronic neuropathic or radicular pain show decreased cognitive performance and this decline is particularly observed in older patients (Moriarty et al., 2011, 2017). This suggests that clinical pain can decrease cognitive function and that this effect is moderated by age. Conversely, studies in patients with dementia indicate that cognitive decline is associated with greater amplitude and duration of pain-related activity in regions associated with sensory, affective and cognitive processes (Summers et al., 2016). Based on these interactions between cognition, pain and age, anodal tDCS may be especially useful in older persons affected by cognitive decline, chronic pain or both (Hsu et al., 2015). Besides, It remains to be determined whether anodal tDCS of the DLPFC may be effective at improving pain inhibition by WM in different clinical populations in which an attentional bias to pain was reported (Eccleston et al., 1999b; Torta et al., 2017a). Another limitation that should be mentioned is that tDCS is not a focal method and other regions and their networks may be stimulated in addition to the DLPFC, over which the anode was placed. There- fore, like in other tDCS studies, the effects reported here cannot be attributed to the DLPFC exclusively.

5. Conclusion

The present study shows that WM and pain inhibition is enhanced by anodal tDCS in older persons. This warrants future studies to examine whether multiple tDCS sessions with cognitive training may produce long-lasting changes in pain regulation and pain symptoms in healthy older persons and patients with cognitive decline or chronic pain.

Author's contributions to the manuscript

1- Zoha Deldar contributed to all aspects of the research.

2- Nabi Rustamov contributed to data acquisition and interpretation.

3- Isabelle Blanchette contributed to experimental design, data interpretation and manuscript preparation.

4- Mathieu Piché contributed to all aspects of the research and obtained funding for the study.

All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors report no financial or other relationship that may lead to any conflict of interest.

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Chapter 4. General Discussion and conclusion

The first objective of my doctoral work was to examine whether pain inhibition by WM engagement can be enhanced by tDCS in healthy young and older volunteers. We hypothesized that anodal tDCS of the DLPFC would improve WM performance, which in turn would improve top-down pain inhibition during performance of a cognitive task in young and older healthy volunteers (Hypothesis 1). We also investigated the interaction between task performance and pain perception and how WM could moderate these dynamics. We hypothesized that performing a WM task could decrease pain in young and older healthy volunteers (Hypothesis 2). We then tested whether pain inhibition by WM depended on descending inhibitory pathways, using the nociceptive flexion reflex (NFR) as an index of spinal nociceptive transmission (Hypothesis 3) (Ladouceur et al., 2017; Piche et al., 2011).

1. Enhancement of working memory and pain inhibition by tDCS

The novel finding of the current work is that pain inhibition by WM was enhanced by anodal tDCS of the left DLPFC during the high load WM condition (2-back task), indicating that anodal tDCS of the left DLPFC increased top-down inhibition of pain by WM. In contrast, applying anodal tDCS while painful stimuli were administered alone without the concurrent cognitive task did not result in pain inhibition. These results imply that anodal tDCS over the left DLPFC might enhance pain inhibition by improving WM. In addition, anodal tDCS improved WM but not NFR inhibition by WM. This suggests that anodal tDCS enhances pain inhibition by improving WM but not by increasing descending inhibition of spinal nociceptive activity. Pain inhibition enhancement may thus be independent of descending modulation. To summarize, anodal tDCS of the left DLPFC may help to improve pain inhibition in young and

older persons (Deldar et al., 2019; Deldar et al., 2018). In the next section, I will describe the meaning of our results in regards to the interaction between the effect of tDCS and demand of the cognitive task by explaining the concept of cognitive effort.

1.1 Interaction between the effect of tDCS and demand of the cognitive task by explaning the concept of cognitive effort

The mean response times of the n-back task were decreased during anodal tDCS over the left DLPFC. This effect was strong in the high WM load condition (2-back task), but was not observed in the low WM load condition (0-back task), for either healthy young and older adults. These results are consistent with an improvement of WM by anodal tDCS of the left DLPFC in healthy young subjects (Andrews et al., 2011b; Brunoni et al., 2014; Hill et al., 2016; Mariano et al., 2016; Mylius et al., 2012b; Saladin et al., 2015; Wolkenstein et al., 2013), and healthy older subjects with involvement of the DLPFC in the central executive system of WM (Awh et al., 2006; Lavie et al., 2006; Lavie et al., 2004; Legrain et al., 2009; Levy et al., 2000; Park et al., 2014; Wager et al., 2014). These results also show that an improvement in WM during more demanding tasks may contribute to increased pain inhibition.

We were able to replicate the results of our first study, which was with healthy young subjects, in our second study, using healthy older persons. The following discussion will thus analyze the results of both studies. We will introduce cognitive effort concept in the following section becouse our findings showed that response times in the 2-back task condition was faster than response times in the 0-back condition. In addition, response times in the 2-back task

conditions decreased by painful stimuli compared to the same condition without pain. Cognitive effort might clarify these results: succeeded in more demanding task could have been associated with investing more effort. Accordingly, tDCS might increase performance in more demanding task by allocating more resources (efforts) to the task. As I briefly discussed our findings in Chapters 2 and 3 (Deldar et al., 2019; Deldar et al., 2018), in the following section I will describe in more depth the interaction between the effect of tDCS, cognitive task demands, and pain inhibition, using the concept of cognitive effort.

1.1.1 Cognitive effort

Cognitive effort is the amount of attentional engagement (i.e. attentional resources) allocated to the performance of a task (Sarter et al., 2006; Westbrook et al., 2015). Better performance on a particular task might be the outcome of higher attentional engagement. In order to clarify the definition of effort, it is important to distinguish it from other similar concepts including attention, concentration, motivation, and task difficulty (Westbrook et al., 2015).

Cognitive effort is not a synonym of attention. For example, top-down attentional processes (i.e. voluntary attention orientation) might be effortful, but bottom-up processes (i.e. involuntary attention orientation) cannot be considered as such (Kaplan et al., 2010; Westbrook et al., 2015). Similarly, the concepts of effort and difficulty are closely related but are not equivalent. The distinction between effort and difficulty can be explained by two different types of tasks: "data-limited" and "resource-limited." Allocating more cognitive resources to

resource-limited tasks (e.g., the n-back tasks used in our studies) can enhance performance in these types of tasks. However, allocating additional cognitive resources would not improve performance in data-limited tasks if performance depends on the quality of data. For example, reading low contrast words within a text can be difficult, but the performance of this task does not require a higher amount of effort compared to reading normal contrast words. Subjects performing this task might consider it difficult but not effortful, as no matter how much effort they might invest to perform the task, they cannot succeed (D. A. Norman & Bobrow, 1975) (Norman et al., 1975). The concept of concentration is also related to effort, but they do not have the same meaning. Sustaining high concentration while performing a task might not always require an investment of much effort to achieve the task. For example, a professional writer might have high levels of concentration while writing but might not need to exert much effort to accomplish this task (Norman et al., 1975; Westbrook et al., 2013). Effort is not a synonym for motivation, either. For example, depending on task requirements, participants can be instructed or motivated to invest either maximum or minimum effort to perform a task (Westbrook et al., 2015). In summary, the concept of cognitive effort is firmly attached to the concepts of attention, difficulty, concentration, and motivation, but they are not interchangeable. Cognitive effort modifies the amount of attentional resources allocated to accomplish a particular task through WM function (Sarter et al., 2006; Westbrook et al., 2015).

Regarding the interactions between cognitive effort, pain perception, and WM, one of the main factors considered in the neurocognitive model of attention to pain is attentional load (Legrain et al., 2009). According to this model, the effects of painful stimuli will be reduced by performing a cognitive task that requires more effort (e.g. 2-back task) (Legrain et al., 2013;

Legrain et al., 2011b; Legrain et al., 2009; Torta et al., 2017a). This pain reduction might be related to the fact that cognitive resources must be allocated to both the selection of goal-directed information (top-down attentional processes) and painful stimuli (bottom-up attentional processes) (Barcelo et al., 2006; Berti et al., 2004; Legrain et al., 2009; McCaul et al., 1985). Therefore, if a cognitive task requires more effort (e.g. 2-back task), less available resources will remain available to process painful stimuli (Legrain et al., 2009; Sarter et al., 2006; Westbrook et al., 2015). Attentional load is determined and limited by WM capacity, which is the ability to store information despite ongoing processing. This is an indication of the limitation of cognitive resources (Barrett et al., 2004; Heitz et al., 2008; Kane et al., 2001; Kane et al., 2003; Lavie et al., 2004; Rosen et al., 1998; Unsworth et al., 2006; Unsworth et al., 2009). In summary, cognitive effort optimizes limited cognitive resources through WM functioning in order to inhibit pain (Sarter et al., 2006; Westbrook et al., 2015).

Regarding the effect of tDCS in this interaction, the outcome of the stimulation protocol will depend on both the effort required by the particular task and the state of the neural network (Miniussi et al., 2013; Paulus, 2011; Roe et al., 2016). In line with this idea, some tDCS studies have proposed that the influence of anodal tDCS is modified by task demands (Legrain et al., 2011b). The availability of cognitive resources is critical, and the effect of tDCS may depend on increasing the availability of cognitive resources, especially when WM is highly loaded (Crombez et al., 1998; Lavie et al., 2004). In conditions with low WM load (e.g. a 0-back task), some cognitive resources remain available, so tDCS may not bring any gain in performance. This explanation may reconcile some of the discrepancies observed between tDCS studies. Taken together, cognitive effort optimizes cognitive resources. Applying tDCS over the left

DLPFC may enhance the accessibility of cognitive resources (i.e. effort) in order to improve cognitive performance and inhibit pain.

We observed enhanced WM function and increased inhibition of pain perception after the application of tDCS over the left DLPFC in both healthy young and older adults, but this result raises the question of whether these two phenomena are strongly associated with each other or not. We cannot conclude without a doubt that the increased inhibition of pain perception was due to WM engagement, and it is thus possible that different processes mediate the two effects. However, we included a pain only condition to confirm whether or not pain can be inhibited by tDCS without a task, and found this was not the case. We also included a 0-back condition in which WM engagement was low. In this case, anodal tDCS did not improve pain inhibition. In contrast, pain inhibition was enhanced by anodal tDCS in the 2-back condition, in which WM performance was also improved. Therefore, we suspect that pain inhibition was enhanced, at least in part, by improvement of WM, although we cannot exclude that these two changes may have occurred independently. Future studies might need to examine brain activity during this interaction through the use of EEG or fMRI. Furthermore, the lack of significant change in NFR amplitude indicates that this interaction relies on a supraspinal mechanism that does not involve descending modulation (Deldar et al., 2019; Deldar et al., 2018). In summary, although we suspect that pain inhibition was improved by the enhancement of WM, we cannot exclude the possibility that independent processes may produce both effects.

2. Interactions between pain and working memory

In the presented studies, the experimental protocol was designed to favor the execution of a cognitive task and the inhibition of pain (see also Chapter 2 and 3) (Deldar et al., 2019; Deldar et al., 2018). The pre-tDCS baseline conditions consisted of pain alone, 0-back with or without pain, and 2-back with or without pain (Deldar et al., 2019; Deldar et al., 2018). The section below discusses the interpretation of the findings concerning WM performance, pain ratings, and NFR amplitude, as well as their interactions with each other.

2.1 Working memory performance during the pre-tDCS baseline

Our findings regarding WM performance of young subjects during the pre-tDCS baseline showed no difference between response times during conditions with pain compared to conditions without pain (Deldar et al., 2018). Moreover, the results in WM performance of older persons during the pre-tDCS baseline revealed that response times were decreased when the 0-back and 2-back tasks were performed with pain, compared with the same conditions without pain (Deldar et al., 2019). Accuracy on the WM tasks was consistent across all conditions for both studies (Deldar et al., 2019; Deldar et al., 2018). These findings imply that salient painful distractors could not affect WM performance during either the 0-back or 2-back conditions, for either young or older adults (Deldar et al., 2019; Deldar et al., 2018). The most probable reason is that rehearsing and updating the features of visual targets by engaging WM was sufficient to avoid a bottom-up shift of attention towards the salient painful distractors (Legrain et al., 2011; Legrain et al., 2013; Legrain, et al., 2009; Soto et al., 2005; Soto et al.,

2008). These findings are in line with those of previous studies in which WM engagement was observed to suppress the effects of painful stimuli (Coen et al., 2008; Legrain et al., 2011; Soto et al., 2008). Indeed, nociceptive signals compete with other sensory signals when entering and being processed by the attentional network because of limited cognitive capacity (Legrain et al., 2009; McCaul et al., 1985). This neural response to specific stimuli can be biased by stimulus saliency (i.e. bottom-up attention processes) (Egeth et al., 1997; Knudsen, 2007; Yantis et al., 1990), or by the relevance of a stimulus to the task goal (i.e. top-down attention processes) (Folk, et al., 1992; Hopfinger et al., 2006; Legrain et al., 2011; Van Damme et al., 2010). The central executive component of WM can be a source of bias (Baddeley, 2012; Legrain et al., 2011; Legrain, et al., 2009) that inhibits the effect of painful stimuli by maintaining task-relevant target features (attentional set) (Crombez et al., 1998; Crombez et al., 2013; Legrain et al., 2009) and maximizing the attentional load of WM capacity (Kane et al., 2001; N. Lavie et al., 2004; Legrain et al., 2009; SanMiguel et al., 2008; Unsworth et al., 2009).

Observations of WM performance during conditions with and without the presentation of painful stimuli might raise questions such as why some studies have found pain inhibition by WM tasks while others did not. Why were response times during the 0-back and 2-back task conditions with painful stimuli decreased compared to the same conditions without pain? Moreover, why were the response times in the 2-back task faster compared to the response times in the 0-back task condition? In the following section I will provide possible answers to these questions.

2.2 Why have some previous studies found pain inhibition by working memory tasks, while others did not?

Some technical and conceptual criteria might affect the interaction between WM function and painful distractors. For example, using different types of cognitive tasks with different cognitive demands, or different or insufficient levels of pain intensity might affect this interaction (Buhle et al., 2010) (see also discussions in chapters 2 and 3) (Deldar et al., 2019; Deldar et al., 2018). In the current studies, we chose an n-back task with different WM loads, to vary the demand on the central executive component (Buhle et al., 2010; Legrain et al., 2013). This requires a continuous update of information for the selection of appropriate responses (Buhle et al., 2010; Jones et al., 2012). Studies that used demanding n-back tasks have obtained similar findings (Buhle et al., 2010; Legrain et al., 2011a; Legrain et al., 2013). whereas studies using tasks with low WM loads (such as the Sternberg task) showed no pain reduction during task performance (Buhle et al., 2010; Houlihan et al., 2004).

2.3 Why were response times during 0-back and 2-back task conditions decreased by painful stimuli compared to the same conditions without pain?

This is a reproducible effect that was reported in our previous study (Deldar et al., 2018). Also, it was reported that when participants prioritize a cognitive task, like the n-back task, RTs are decreased (Erpelding et al., 2013). However, it is obvious that if participants would prioritize pain stimuli, the effect would be opposite. Although we did not measure the effect of cognitive

effort in these studies, it seems plausible that participants might invest more effort to perform more demanding tasks, leading to the allocation of more cognitive resources to performance of the tasks and greater pain inhibition.

2.4 Why were response times in the 2-back task condition faster than response times in the 0-back condition?

Faster response times in 2-back vs. 0-back task conditions is a well-known effect that has been previously reported (Legrain et al., 2011; Legrain et al., 2013). A possible explanation may be that in the 2-back condition, visual targets have been processed two trials earlier and the response has already been selected and held ready for use in WM. However, the visual targets in the 0-back conditions must be processed before the response can be selected and provided. Moreover, accuracies in the 0-back conditions were increased compared to the 2-back conditions in both groups, indicating that performing the 2-back task was more difficult than performing the 0-back, independently of age.

2.5 Pain ratings during the pre-tDCS baseline

The 0-back and 2-back task conditions produced the expected reduction in pain ratings, consistent with the finding that response times were unaltered by pain. These findings are also consistent with results of previous studies (Bingel et al., 2007a; Buhle et al., 2010; Buhle et al., 2012; Coen et al., 2008). Indeed, in the present studies, WM performance was improved while pain perception decreased in both 0-back and 2-back task conditions involving WM

engagement. However, there may be experimental conditions or daily situations in which pain is prioritized, resulting in reduced cognitive performance. For example, patients with fear of pain or with chronic pain may be hypervigilant to pain (Van Damme et al., 2010b), which could bias attention towards pain processing at the expense of cognitive task execution.

2.6 NFR amplitude during the pre-tDCS baseline

The lack of NFR amplitude inhibition in the high WM load condition. Increased WM load and decreased pain perception have previously been found to be related to reduced NFR amplitude although a dissociation between spinal activity and pain perception has also been reported (Danziger et al., 1998a; Defrin et al., 2007b; Piche et al., 2009a; Terkelsen et al., 2004b). In regards to our results, we postulate that the more demanding task produces disinhibition of spinal nociceptive activity in order to maintain protective reflexes while WM shields cognition from nociceptive signals in the brain to allow for optimal task performance.

Taken together, our findings of increased WM performance and decreased pain perception in these studies suggest that limited cognitive resources are dynamically distributed between these two processes. In the context of our research, performing more effortful WM tasks contributes to greater allocation of attentional resources to WM and results in less cognitive resources remaining available for the processing of painful stimuli.

3. Limitations and future considerations

There were some limitations in the presented studies. The first concerns differences in the sensations perceived during anodal versus sham tDCS, and the potential involvement of a placebo effect. It is important to describe how we confirmed the success of our double-blind procedure. While the sensations of anodal and sham tDCS stimulation are different, participants were unaware that tDCS stimulation could vary between sessions or that we were testing two different types of stimulation (i.e. they wouldn't know that the sham is sham, they would only know it felt different). They were informed that they might feel itching or burning, but they were not told that the presence or intensity of itching or burning was in any way correlated with the effects of the stimulation on task performance or pain perceived. Therefore, participants did not expect a placebo condition or a condition with stimulation that was more or less effective. In fact, the tDCS stimulator that was used is specifically designed to limit the placebo effect by employing the same ramp-up at the beginning of the stimulation (Deldar et al., 2019; Deldar et al., 2018). Future studies need to measure the sensation in order to confirm whether participants have similar or different sensations during anodal and sham tDCS. For example, Saruco and colleagues asked participants after sham and anodal tDCS sessions whether they received a real stimulation. Participants could answer by choosing "Yes," "No," or "I do not know." Conformity Chi-squared test was performed on the proportions of participants' "Yes" and "No" answers for each brain stimulation session against proportions corresponding to the chance level (50%). The conformity Chi-squared test was not statistically significant (all $p > 0.05$), indicating that Participants were blind about the effect of sham and anodal tDCS sessions (Saruco et al., 2017).One possibility that should be considered to explain the improvement of WM by anodal

tDCS is that the sensation produced by anodal tDCS on the scalp may increase alertness, thus leading to improvement of reaction times. However, this possibility is unlikely since the same effect should apply to the performance in the 0-back task, which was not observed.

Another limitation that should be cited is that tDCS is not a focal method; in addition to the targeted region – the DLPFC, other regions may be affected by anodal stimulation. Therefore, as in other tDCS studies, the effects cannot be attributed definitely to the DLPFC (Woods et al., 2016a; Woods et al., 2015). However, based on several brain simulation studies, the left DLPFC is stimulated with montages similar to that used in our studies (Andrews et al., 2011a; Fregni et al., 2005; Mariano et al., 2016; Wolkenstein et al., 2013).

There are also a few limitations related to research on pain inhibition via WM engagement. First, we asked participants to rate their pain after each painful condition (i.e. 0-back with pain, 2-back with pain and pain alone conditions). The act of rating pain can make the painful stimuli relevant for the participant's behavioral goals (Torta et al., 2017b). In addition, it has been shown that rating pain directly after painful stimulation more reliably reflects the pain experience compared to pain ratings were provided at the end of the painful conditions, meaning they might reflect pain memory rather than the direct pain experience. However, the goal of our studies was to assess pain modulation; therefore, we used the pain rating method. Moreover, we asked participants to rate their pain after each painful condition in order to avoid any interruption while performing the cognitive task.

Having discussed these limitations, I will now propose some suggestions regarding future work.

First, regarding the effect of WM engagement on pain inhibition, there are still some specific questions to address. For example, individuals with low WM capacity are less able to use attentional control over WM processes (Fukuda et al., 2016). This may result in greater attentional shifts towards distractors, and thus the storage of more distracting information with a limited-capacity compared to individuals with high WM capacity. Although these individual differences have been highlighted through a critical link between WM capacity and attentional control (Fukuda et al., 2016), it is unclear how attentional control ability can modulate pain perception and the impact of individual differences on this process. By identifying individuals with low WM capacity, it may be possible to train people to encode and store non-painful information in WM more selectively. Therefore, future work should evaluate the effect of WM performance on pain inhibition in people with both high and low WM capacities by assessing WM capacity of participants even before starting experimental protocol. It was not possible to do this in our studies because of our small sample size also; we did not separate participants before running the main experimental protocol. Moreover, it might be interesting to examine the effect of tDCS over DLPFC on pain inhibition in people with high WM capacity compared to people with lower WM capacity (see **Figure 19**).

Second, previous studies have shown that motivation affects performance on competing tasks (Inzlicht et al., 2012) and pain perception (Van Damme et al., 2010b; Verhoeven et al., 2010). Therefore, it might be interesting to evaluate the effects of motivation in the current paradigm or to reward participants for better task performance and observe the effects of rewards on pain perception. Moreover, as we previously mentioned the impact of cognitive effort on the

performance of a cognitive task in this chapter, future studies might need to evaluate the effects of cognitive effort and cognitive fatigue according to a NRS scale (i.e. 0 = no effort/fatigue; 100 = extreme effort/fatigue) at the end of each condition (see **Figure 19**) (Silvestrini et al., 2013).

Future studies might need to consider some updates in the neurocognitive model of attention to pain. We suggest that the balance between top-down, bottom-up selections and WM process might be affected by some factors. 1) individual differences in working memory capacity (high vs. low capacities) (Fukuda et al., 2016); 2) in attentional control ability (Fukuda et al., 2016); 3) in the cognitive effort: the intensity or amplitude of mental and/or physical actions in order to achieve a goal. Some people enjoy performing tasks, which need to think deeply. They invest more cognitive effort to perform them for their own sake. Whereas, others might avoid mental exertion whenever they can. People who consider the higher value to the mental effort, require fewer motivations to perform it. They seek it out instead of avoiding it (Inzlicht et al., 2018; Sandra et al., 2018; Westbrook et al., 2015). 4) in motivation (Van Damme et al., 2010b); 5) in their learning histories (Eccleston et al., 1999a); 5) in pain coping strategies (Erpelding et al., 2013; Kucyi et al., 2013); 6) in psychological factors (Torta et al., 2017a); 7) in emotional status of the person (Sussman et al., 2016; Vanlessen et al., 2014); 8) in mental health (e.g., anxiety and depression disorders) (Bagnato et al., 2018; Torta et al., 2017a) (see **Figure 19**).

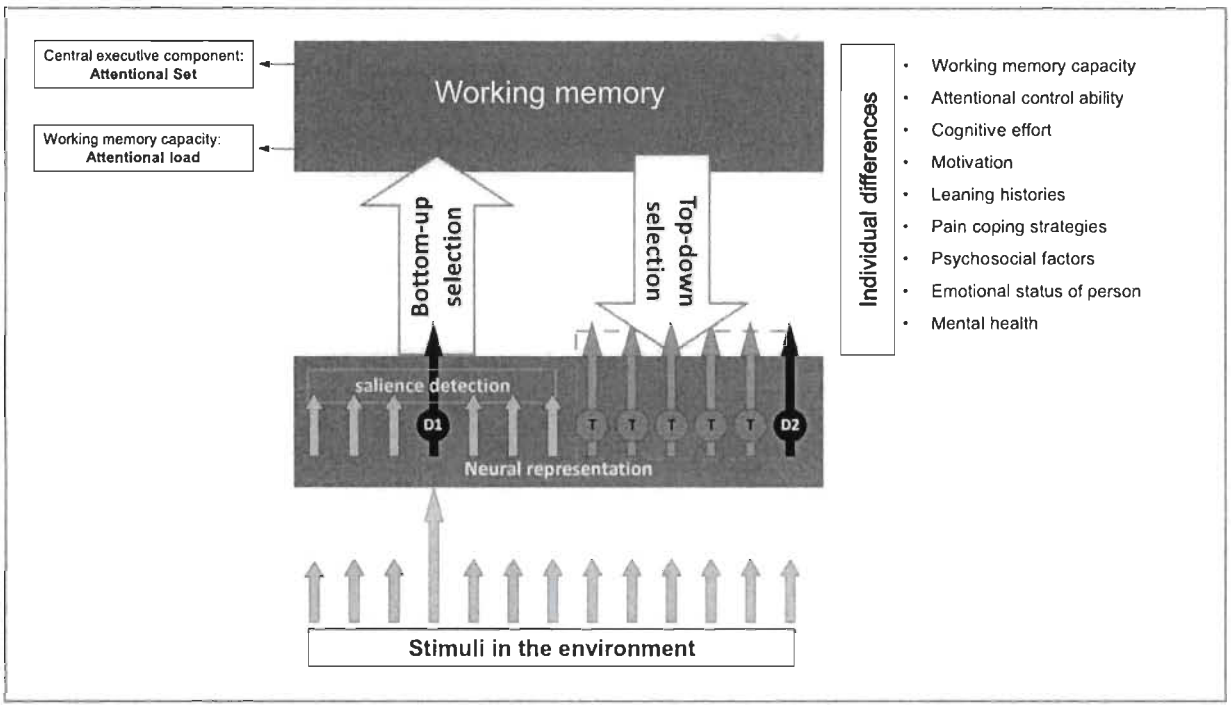

Figure 19. Future consideration in the neurocognitive model of attention to pain.

Third, the interaction between pain inhibition, WM engagement, the effect of tDCS, and brain activity is unclear. A future study might examine this interaction by adding EEG and using high-definition tDCS with small multi-electrode arrays (Edwards et al., 2013; Saturnino et al., 2015).

Fourth, further research is needed to examine the effects of repeated tDCS sessions (Jones et al., 2015a), and the long-term effects of tDCS on pain inhibition and WM engagement, and the brain mechanisms behind this process. Another topic to explore is how various new paradigms and pain conditions can be applied to extend the benefits of tDCS.

4. Significance of research: from experimental to clinical implications

Some considerations must be acknowledged before generalizing our experimental findings to the clinical context. First, experimental pain does not adequately represent pain in real life. Second, the healthy and pain-free young and older participants in our studies behave differently from chronic pain patients, who commonly suffer from anxiety and depression (Dersh et al., 2002), sleep disorders, declines in every job-related activity (Choiniere et al., 2010), and clinical problems with the central mechanisms of pain regulation (Woolf, 2011). However, our findings might be extended to some clinical contexts, which I will discuss in the next paragraph.

As previously stated, there is an interaction between cognitive performance, increased age, and pain perception. Chronic pain conditions may progress parallel to age-related cognitive decline. Moreover, pain is related to brain alterations, which may be associated with the cognitive decline present in older adults (Moriarty et al., 2017; Oosterman et al., 2013; Oosterman et al., 2016). For example, some studies have showed that cognitive performance was decreased in patients with chronic neuropathic or radicular pain, and this decline was mainly observed in older pain patients (Moriarty et al., 2011; Moriarty et al., 2017). Studies in dementia patients have also provided evidence of a potential effect of age-related cognitive decline on pain. One study found that Alzheimer's patients had greater amplitude and duration of pain-related activity in sensory, affective, and cognitive brain regions (Hsu et al., 2015; Summers et al., 2016). This result was correlated with sustained attention to the noxious stimuli compared

to healthy participants. Considering this potential interaction, the use of one or more sessions of anodal tDCS with the aim of improving cognitive performance and in turn inhibiting pain might be particularly useful for individuals who are suffering from cognitive decline and/or pain.

Moreover, evidence has suggested that chronic pain patients who performed better in a task with distraction showed better pain inhibition, which is consistent with our findings (Buhle et al., 2010; Deldar et al., 2019; Deldar et al., 2018; Schreiber et al., 2014). This implies that improving performance in cognitive tasks by applying one or more sessions of anodal tDCS might contribute to pain inhibition in people who are suffering from acute or chronic pain.

Evidence also supports an interaction between pain and depression (Bagnato et al., 2018; Doan et al., 2015; Zis et al., 2017). People who suffer from major depression experience more pain in their lives (e.g, they report more pain in experimental conditions) (Avery et al., 2014; Bagnato et al., 2018; Saariaho et al., 2013; Wilson et al., 2014; Zis et al., 2017), while chronic pain patients report more depressive symptoms compared to control populations. Moreover, evidence have reported abnormal activity in certain brain regions, including the DLPFC, in both depressed patients and those with chronic pain (Seminowicz et al., 2017). Treatment of depression in chronic pain patients may be beneficial as it could result in improved quality of life and increased physical exercise, social interaction, and adherence to pain-reduction interventions (Downar et al., 2013; Seminowicz et al., 2017). Therefore, studies looking at the application of anodal tDCS to the DLPFC as a treatment for depression might also observe a reduction in chronic pain symptoms (Seminowicz et al., 2017).

I have acknowledged some limitations in our research, which must be considered in order to apply our experimental protocol to clinical populations. It is essential to remember that chronic pain is a process which always has a beginning, and thus it is vital to determine which factors can affect this process before it becomes chronic and how to best manage it. Finally, our knowledge about brain stimulation and cognitive pain modulatory techniques is limited, showing the essential need for the development of new chronic pain management tools.

5. General conclusions

In conclusion, this project has revealed the interactions between WM function and pain inhibition, and their enhancement by tDCS. In two studies, we found that anodal tDCS inhibited pain by improving WM performance and that this pain inhibition by WM improvement was independent of the descending spinal nociceptive inhibitory system (Deldar et al., 2019; Deldar et al., 2018), These interactions have important implications for interventions aimed at patients suffering from pain and/or deficits in WM performance (e.g. chronic pain, dementia, and major depression). The identified targets (i.e., interactions between WM, pain, aging) may contribute to the development of better clinical tools, including drug-based or alternative therapies (including brain stimulation techniques), to minimize pain. We hope that sharing these findings will contribute to future efforts both to alleviate pain and improve cognitive deficits.

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